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ARCHIVES OF PATHOLOGY
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VOLUME 1 APRIL, 1926 NUMBER 4

BILATERAL CAROTID ARTERITIS*

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Recent observations indicate that the arteries may be the seat of morbid processes, particularly inflammation, more frequently than is ordinarily believed. I touched on this subject in 1921 [1] in describing certain unknown forms of arteritis and in discussing at the same time endarteritis and periarteritis nodosa. The subject has received increased attention by the demonstration of arterial inflammations in infectious diseases, particularly typhus fever, and by the demonstration of microbes in the endothelial cells of the capillaries in the skin in infections with hemorrhages and eruption in the skin,[2] such as epidemic meningitis and gonorrhea.

Not long ago I had the opportunity to examine a woman, aged 28, who died from croupous pneumonia on the ninth day. During the last day a herpetic eruption appeared on the chest and abdomen in the form of blisters as large as a pinhead and larger. In sections the epithelial cells were spread apart by serous fluid. In this fluid as well as in the cells were many gram-positive cocci resembling pneumococci, and in the small arteries under the vesicles were large masses of similar cocci either free in the lumen or within the endothelial cells. These appearances indicated clearly that invasion of pneumococci led to the formation of vesicles about which there was little sign of inflammation.

It has also become established more and more that various intoxication may be associated with important changes in the arteries, usually, however, of a necrotic or degenerative sort.

Recently I examined a case in which a thrombo-arteritic process was the essential lesion, and on account of its peculiarities and localization it may be worth while to describe the condition in some detail.

CASE 1.—A woman, aged 37, of a healthy family, who had had no abortions, and whose husband and 14 year old son, her only child, were in good health, in 1913-1914, when 26 years old, spent some time in a hospital on account of neph-

*From the Pathologic Anatomic Institute of the University of Oslo.

1. Harbitz, F.: Unknown Forms of Arteritis with Special Reference to Their Relations to Syphilitic Arteritis and Periarteritis Nodosa, Am. J. Med. Sc. **163**:250, 1922.

2. Bruusgaard and Thjotta: Gonococcus Meningitis and Purpura, Norsk. Mag. f. Lægevidensk. **85**:809, 1924.

ritis after scarlet fever. The present illness was noticed first in the spring of 1923; there was then a glittering before the eyes lasting about five minutes and recurring during the summer and autumn. At Christmas, 1923, she had an attack of dizziness with shadows before the eyes and jerkings in the arms and legs; it felt as if the eyes were being drawn into the head; at this time she was nervous and palpitations would come on easily; an ulcer appeared in the nose and extended through the septum, resulting in perforation ("ulcus perforans septi nasi simplex"). The Wassermann reaction was negative in June, 1924. In the spring of that year there was a feeling of weakness in the left arm and the right leg. She would fall, was tired, had noises in the ears and poor vision. At the time of her entrance into the hospital in June, 1924, the palpebral fissures were large; there was no definite radial pulse, but the arteries were palpable and not rigid; there was a systolic blowing over the apex. In the middle of August, she had a transitory paresis of the left arm, and fell again, but without losing consciousness; there was burning pain in the orbits and the eyes seemed to be drawn back, but roentgen-ray examination of the cranium gave only normal appearances. In October, there was a definite atrophy of the right half of the face. The pulse rate was from 100 to 136. The diagnosis was exophthalmic goiter, facial hemiatrophy and nephritis (trace of albumin once). As there was now found a cataract in the right eye, the patient was transferred to the division for eye diseases, where she died on Dec. 16, 1924.

During the previous June, atrophy of the stroma of the iris had been demonstrated by the ophthalmoscope; the veins in the right eye were then dilated, the blood stream small. In August, there was a peculiar finely meshed vascularization of the pupilary margin on the temporal side. The blood moved slowly in the veins, and movement was barely demonstrable in the arteries; the lumens of the vessels were irregular, and there were small hemorrhages in both retinas.

On November 11 it was noticed that the facial atrophy was becoming more pronounced; the lens was turbid; ophthalmoscopically there were seen large dilated veins, irregular arteries, a few grayish-white flecks around the macula, and it was thought that there might be an angiosclerosis of the retina.

On December 12, she was stricken with coma and paralysis of the right arm and leg, and died after a few days.

Necropsy.—The body was well nourished; there was no edema or eruptions; the skin of the face was smooth and tense, without wrinkles; the orbital margins were prominent. The pericardium was normal; the heart weighed 470 Gm.; the valves, lining and myocardium were free from changes; there were a few small sclerotic spots in the coronary arteries which were otherwise normal. The lungs were somewhat congested, and in the left lower lobe there was a beginning pneumonia. The ascending aorta was soft and elastic, and there were no changes in the arch except that the place of origin of the larger branches was somewhat narrower than usual, particularly in the case of the left carotid artery; arteria anonyma was also narrower than usual at its origin, and the narrowing increased so that at a point 1.5 cm. above the origin the lumen admitted only a small probe, and the walls were definitely thicker than normal; this condition continued into the subclavian and right carotid arteries, which were completely obliterated, thin and narrow, filled by a grayish thrombus. In the right common carotid artery, there was thrombosis throughout into the internal carotid, whereas the external carotid was free and open. The left common carotid was obliterated completely from its origin to the internal carotid which in this case was open. The right vertebral artery was thrombosed completely from its origin on; the left verterbral artery was partially occluded at its origin. The brain and eyes consequently

received arterial blood only through the left vertebral and possible small anastomoses. The left subclavian was also obliterated about 1.5 cm. above its origin and filled with thrombus for about 1 cm. The brachial artery was open and normal. All the large veins in the chest and neck were normal as were also the radial, femoral and anterior tibial arteries. The descending thoracic and abdominal aorta was greatly changed and formed a stiff inelastic tube, which was calcified here and there; the wall was finely wrinkled, with yellowish plaques; but the intima was intact, and there were no scars and no dilatations, but the origins of some of the intercostals were closed. Below the division of the abdominal aorta the walls were soft and free from changes, but the celiac and inferior mesenteric arteries were changed in the same way as the aorta and were also somewhat

Fig. 1.—Small artery in cutis with cocci resembling pneumococci in lumen and in endothelial cells; × 1200.

narrowed; the renal arteries were narrowed a little at their origin, but they were otherwise normal. The basilar and principal cerebral arteries were not changed.

The thyroid weighed 35 Gm. and was normal in consistence and structure; the thymus was rather large and flat. The pharynx and esophagus were normal. The peritoneum was normal; the spleen (180 Gm.), liver (1,570 Gm.), pancreas, stomach and intestines were normal; the kidneys (310 Gm.) showed indistinct markings; the suprarenals (20 Gm.) were deep yellow in the cortex; in the left ovary there was a cyst as large as a hen's egg; the uterus was normal.

There were no changes in the cranium; in the longitudinal sinus posteriorly there was an occluding thrombus which extended into the transverse sinus on

both sides; the pia-arachnoid had dilated veins, not adherent; the arteries at the base of the brain were normal; at the opening of the right carotid artery there was a sclerotic spot, but the left carotid was normal; in the left sylvian artery were two, rather firm, fresh thrombi, and there was a poorly defined softening of the central convolutions and adjacent parts of the frontal and parietal lobes as well as of the medial surface and to a slight degree of the temporal lobe, but the basal ganglions and the central white matter were normal.

Fig. 2.—Occlusion of arteries of neck.

Anatomic Diagnosis.—Scleroris (arteritis?) of the thoracic and abdominal aorta, arteria anonyma, right and left subclavian, vertebral, both common carotid and right internal carotid arteries with stenosis and thrombosis; thrombosis of the left sylvian artery with cerebral softening; thrombosis of longitudinal and transverse sinuses; facial atrophy and atrophy of the eyes with cataract; hypertrophy of

the heart; bronchopneumonia; splenic swelling, parenchymatous degeneration of the organs; a cyst of the left ovary.

Microscopic Examination.—The left common carotid artery showed fibrous thickening with large inflammatory infiltrations along the vasa vasorum; the infiltrations consisted of lymphocytes and did not contain any giant cells; the muscular coat was indistinct on account of the infiltrations of lymphocytes. The media was partly separated from the intima by retraction along the internal elastic layer, and the whole central part composed of the intima and the obturating mass consisted of a vascular fibrous tissue with some cell infiltration; the vessels were rather large, had thick walls, and the intima was often so thick as to leave only a small slitlike opening, and in some cases the lumen was closed completely.

The right common carotid showed the same changes as the left but in somewhat less degree, the intima being thick and penetrated by large vessels with small lumens, and there were no thrombotic remains. In the left internal carotid there were small infiltrations in the adventitia, which was retracted from scar formation; there were small infiltrations in the media and a great thickening of the intima with marked narrowing of the lumen; in the right internal carotid there were no infiltrations in the adventitia and media, but the intima was thickened, the lumen narrowed and filled with a red thrombus in the early stages of organization.

Sections from a wrinkled area in the arch of the aorta showed extensive infiltrations, especially in the adventitia, less marked in the media, some being sharply defined, others diffuse; the infiltrations consisted of lymphocytes and plasma cells. The changes were most marked at the junction of the middle and outer coats. The same changes were present in the descending aorta, but somewhat less marked. In no cases were there any giant cells or definite gummas. The abdominal aorta, the inferior mesenteric, the femoral and radial arteries appeared normal, and there were no changes in the walls of the left sylvian arteries. The corpora quadrigemina with sylvian aqueduct and parts of the pons, including the nuclei of the trochlear and the oculomotor nerves there, showed no changes.

One eye was examined. There was atrophy of the iris and ciliary processes and muscle, with venous hyperemia in the ciliary body; in the retina there were numerous old and recent hemorrhages, but there were no changes in the retinal arteries; the lens showed obvious cataracts. The changes in the eyes were secondary owing to thrombosis in the carotids and vertebrals and insufficient collateral circulation, with venous congestion, hemorrhages, atrophy and degeneration of the structures in the eye. The arterial occlusion also explains the atrophy of the face.

The kidneys showed hyperemia and some degeneration, but the arteries were normal; the hypophysis, the parathyroids, the sympathetic nerve and ganglion in the neck were normal; the same was true of the liver and spleen.

Comment.—We are dealing here principally with a bilateral disease of the carotids with narrowing and thrombosis. The thrombi were not recent because far advanced in organization and vascularization. In view of the marked inflammatory changes in the walls of the vessels there can be no doubt but that the arteritis was primary and the thrombosis secondary. This view is supported by the severe inflammatory changes in the thoracic aorta in which, however, there were no thrombi. The changes in the eyes were of atrophic and degenerative nature, dependent without doubt on the bilateral process in the internal carotids

Fig. 3.—Section of left common carotid; × 15.

Fig. 4.—Section of organized thrombus with blood vessels; × 55.

and the occlusion of the vertebrals. From the anatomic point of view, there was an arteritis of the aorta, and of some of its principal branches, particularly the carotids, with secondary thrombosis. The problem is, what was the cause? In the first place, it seems clear that endarteritis obliterans (Friedländer) or productiva (Orth) can be excluded. This is a process in which there is an increasing thickening of the arterial wall with thrombosis, narrowing and finally obliteration, with secondary disturbance of nutrition, and, when the arteries in the extremities are attacked, possibly necrosis and gangrene. The disease occurs in young persons and may be symmetrical. It is regarded as an entity of unknown nature; this was the view of Billroth and V. Winiwärter. It has also been regarded as a primary thrombosis with secondary changes in the vessel wall. Others have claimed that there are primary changes in the arterial wall in which a vascular connective tissue develops involving the intima and other layers, but without hyaline degeneration or calcification as in arteriosclerosis. Gerlach [3] has described a gangrene of the legs in a man 19 years old. In one amputated leg the arteries and veins were thrombosed, and the arteries presented changes of a beginning sclerosis without any evidences of arteritis. He called the process endarteritis obliterans and regarded it as the first stage of a presenile angiosclerosis.

Recently I examined the arteries in the amputated parts from the following two cases of spontaneous symmetrical gangrene.

CASE 2.—A German (not Jewish) aged 39, a barber, of a healthy family, for about ten years had had symptoms of arterial changes in both legs. There were no indications of syphilis or diabetes and no overuse of alcohol or tobacco. In 1915 he had had pain in the left big toe, and it had been amputated; later the second toe, then the middle of the foot and finally the leg were amputated; in 1921, pain developed in the right big toe and later gangrene, necessitating amputation in 1925; but the gangrene continued, and a few months later it was necessary to amputate through the thigh; only a few ligatures were required. It was difficult to feel and to count the radial pulse. In the arteries of the amputated parts there were no signs of inflammation or sclerosis; in one or two places the intima was somewhat irregularly thickened, and in such places the tissue was cellular with a homogeneous hyaline intercellular substance and little elastic tissue.

CASE 3.—A sawmill laborer, aged 37, had symptoms of angiospastic gangrene in the feet with a marked feeling of coldness in the toes as well as the fingers. There were no indications as to the cause, and repeated amputations became necessary. In this case also there were no signs of inflammation or sclerosis in the vessels, only contraction with thrombosis in certain vessels.

The cause of these remarkable juvenile affections is obscure. Syphilis may be excluded. Preceding infections, such as influenza and pneumonia, do not seem to play any rôle. Excessive use of tobacco has been blamed, but without good reason except in a few cases. A neuropathic or angiopathic constitution has been urged as the cause, and cases

3. Gerlach: Ueber juvenile Gangrän, Frankfurt Ztschr. f. Path. **15**:243, 1914.

like these have been paralleled with Raynaud's symmetrical gangrene the cause of which appears to be various. The fact that the disease may occur in several children of the same family, indicating a hereditary element, has been advanced in favor of the hypothesis that it is a constitutional disease. This hereditary tendency has been observed particularly among immigrated Polish and Russian Jews in the United States by Buerger,[4] who has had under observation not less than forty such cases of thrombo-arteritis and thrombophlebitis (thrombo-angiitis obliterans), and who has examined the nerves and blood vessels both macroscopically and microscopically in twenty-seven cases. He found in the arteries as well as in the veins changes of an inflammatory nature, including large foci of polymorphonuclear leukocytes besides giant cells; but he is inclined to consider the thrombosis the primary change in the disease, the thrombi later becoming organized in the usual way with large newly formed vessels. Buerger thinks the process is primary in the arteries and that the veins become involved later; the disease may involve also the upper extremities, and nodules may develop in the skin. This disease reminds one of observations in Japan where Haga observed spontaneous gangrene in thirty-seven persons, mostly men between 38 and 47 years of age. Haga[5] found cellular infiltrations in the vascular walls and assumed that syphilis was the cause.

In connection with this matter I referred also to the numerous clinical observations of intermittent claudication (Erb, Charcot)—dysbasia angiosclerotica—a disease that usually develops in older persons and depends on sclerosis in the arteries of the lower extremities with narrowing and secondary thrombosis. This morbid process in the arteries of the lower extremities hardly corresponds to the condition in the case now described. In the first place, the localization in the carotids is different, and there is also in this case a well marked inflammation extending more or less symmetrically over both carotids. What is the nature of this inflammatory process? Syphilis can be excluded as without any basis in the clinical history; the ulcer in the nose was not regarded as syphilitic; and in the necropsy nothing was found suggesting syphilis, while in form and extent the microscopic character of the vascular lesion in no way suggests a syphilitic origin.

What is the nature of the arteritis? While it would be natural to assume that it might be infectious, it was not possible to demonstrate any microbes of any kind in the affected vessels. At present very little is known about the nature of such processes, but accumulating observations indicate that microbes of various kinds may localize and cause

4. Buerger: The Veins in Thromboangitis Obliterans, J. A. M. A. **52**:1319, 1909.

5. Haga: Ueber spontan Gangrän, Virchows Arch. f. path. Anat. **152**:26, 1898.

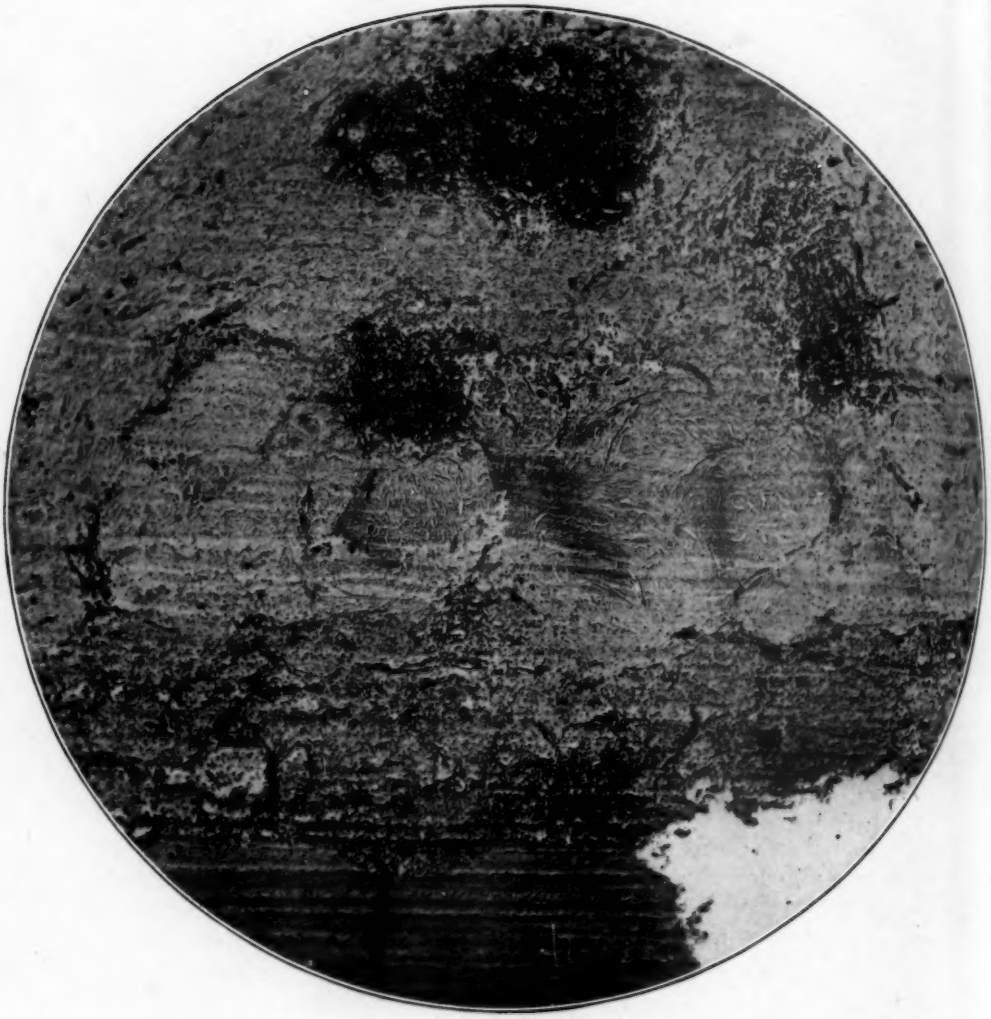

Fig. 5.—Section of arch of aorta; × 40.

Fig. 6.—Cell infiltration in aortic adventitia; × 200.

changes in the arterial wall. I have referred to Buerger's thromboangiitis and Haga's observations, and in addition there are descriptions of arteritis in various infectious diseases with microbes present in the wall of the arteries, notably in typhoid fever, in scarlet fever, in puerperal infections, in acute rheumatic fever and in pneumonia as well as in other infections. Syphilitic arteritis must always be considered, and many remarkable cases and localization of this form have been described, as for instance bilateral syphilitic femoral thrombo-arteritis and multiple arteritis with demonstrations of spirochetes.[6] Of great interest is the case of aortitis in a woman, aged 41, following influenza, described by Beneke.[7] Here were peculiar scars in the aorta and its principal branches with periarteritis, necrosis in the media and sclerosis in the intima. Beneke assumes that following the influenza a streptococcus infection occurred in the adventitia with extension into the other coats. Something similar may have occurred in the case I have described. The symmetrical localization in this case with the resulting clinical picture is remarkable. The following case may be of interest in connection with this question.

CASE 4.—A man, aged 57, had a stroke with paralysis on the left side, and three months later a second stroke followed by a third stroke which resulted in death some seven months later. There was a shrunken area of softening in the left temporal lobe, and part of the occipital and posterior branches of the sylvian artery were changed into fibrous cords. In the right hemisphere there was a large fresh area of softening in the anterior part, including the frontal lobe and part of the parietal lobes and extending inward into the internal capsule. The heart weighed 440 Gm., but did not present any special changes; in the aorta were areas of sclerosis without calcification; just below the branching of both common carotid arteries was a marked sclerosis with thick calcareous plates, thrombosis and obliterations, and the right internal carotid was thrombotic for from 3 to 4 cm. upward from its beginning, while the left internal carotid was narrowed and thrombotic for about 1 cm. Microscopically there were no signs of syphilis, the changes being of a sclerotic nature. In this case the vascular lesion must be regarded as an arterial sclerosis at a comparatively early age; while there is no definite arteritis, the symmetrical distribution of the lesions is similar to that in the first case. Severe sclerosis in the carotids and their branches is not unusual, but as a rule the lesions are not so symmetrical as in the case just described.

SUMMARY

A case of bilateral carotid arteritis with thrombosis is described, and the question is raised whether it concerns a distinct form of arterial disease.

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6. Lignac: Thromboarteritis multiple luetica, Centralbl. f. Path. **35**:661, 1925.
7. Beneke: Ein eigenthümlicher Fall schwieliger Aortitis, Virchows Arch. f. path. Anat. **254**:723, 1925.

GRANULOMA VENEREUM (INGUINALE)

STUDIES ON THE ETIOLOGY AND PATHOLOGY *

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AND
SAMUEL M. PECK, M.D.
NEW YORK

Granuloma venereum as an entity was first described by Conyers and Daniels.[1] The histologic findings in this disease were well brought out by Galloway.[2] The first suggestion of a specific etiology is accredited to Donovan,[3] who described epithelial cell parasites belonging to the gregarian order of *Sporozoa*. Donovan's findings have been supported by many others who accepted the term of Donovan bodies. Carter,[4] and Symmers and Frost [5] among others, believed that they were *Protozoa*.

Several workers have cultured an organism from the lesions of granuloma venereum—Flu,[6] Aragao and Vianna,[7] and Walker [8]—which they thought belonged to the Friedländer group. The behavior of their organisms in animal experiments indeed indicated a type of that group, especially as they failed to reproduce venereal granuloma in animals. As a matter of fact, not sufficient proof has as yet been offered by any of the previous workers to establish any claim for the etiologic rôle of the organisms which they have described and grown from the lesions of granuloma venereum.

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* From the Strecker Memorial Laboratory, New York City Hospital, Dr. Leon H. Cornwall, Director.

1. Conyers, J. H., and Daniels, C. W.: The Lupoid Form of the So-Called Groin Ulceration of this Colony, Brit. Guiana M. Ann. **8**:13, 1896.

2. Galloway, J.: Ulcerating Granuloma of Pudendum, Brit. J Dermat. **9**: 133, 1897.

3. Donovan: Ulcerating Granuloma of the Pudenda, Ind. M. Gaz. **40**:414, 1905.

4. Carter, M.: Ulcerating Granuloma of the Pudenda a Protozoal Disease, Lancet, Oct. 15, 1910, p. 1228.

5. Symmers, D., and Frost, A. D.: Granuloma Inguinale in the United States, J. A. M. A. **74**:1304 (May 8) 1920.

6. Flu, P. C.: Die Ätiologie des Granuloma venereum, Arch. f. Schiffs- und Tropen-hygiene **15**:481, 1911.

7. Aragao, H. de B., and Vianna, G.: Untersuchungen über das Granuloma venereum, Mém. de Inst. Oswaldo Cruz. **5**:211, 1913; Notes on Granuloma Venereum, New Orleans M. & S. J. **70**:369 (Oct.) 1917; Microbe of Venereal Granuloma, Brazil-Med. **33**:74 (March 8) 1919.

8. Walker, E. L.: Etiology of Granuloma Inguinale, J. M. Res. **37**:427 (Jan.) 1918.

Cornwall and Peck [9] have recently published preliminary studies of this disease, and our paper is a continuation of the work since that time, with final conclusions. Studies on a larger number of cases have modified some of the statements made in the previous paper.

The present work includes the three cases previously reported by Cornwall and Peck and four new cases. The clinical side will be reported in another paper, in which will be given diagnosis, allergic diagnostic tests and the results of specific vaccine and tartar emetic therapy.[10]

MORPHOLOGY OF THE ORGANISMS IN SMEARS

Smears from the thoroughly cleaned surface of the granulomatous lesions showed a large number of red blood cells, neutrophilic and eosinophilic leukocytes. There were also a few plasma cells and a varying number of lymphocytes. Isolated large cells with large round, oval

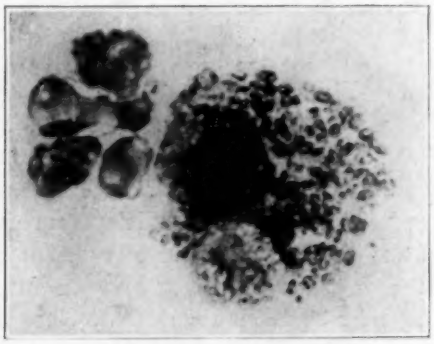

Fig. 1.—Oil immersion photomicrograph of smear from the lesion showing a mononuclear phagocyte containing organisms and a plastine body; Giemsa stain.

or bean-shaped nuclei were also seen. Organisms of a variable morphology were present, resembling cocci, diplococci and bacilli.

Many of the diplococcus forms were surrounded by a halo. Organisms occurred singly and in dense clusters in and outside of cells. Many of the bacilli contained one or more inclusion bodies. The intracellular forms in polymorphonuclear cells were pleomorphic and often showed masses at or near the poles that had an affinity for nuclear dyes. The larger mononuclear cells contained forms that were mostly like bacilli. The bodies of the bacilli stained faintly, with the exception of small

9. Cornwall, L. H., and Peck, S. M.: Etiology Granuloma Inguinale, Arch. Dermat. & Syph. **12**:613-628 (Nov.) 1925.

10. Goldzieher, M.: Granuloma Inguinale, Arch. Dermat. & Syph., to be published.

inclusions that behaved tinctorially like nuclear substance; that is, were basophilic (fig. 1).

The bacilli sometimes became swollen and assumed the forms of giant cocci containing one or two granules. These forms have been described by many as encapsulated organisms, but we were unable to demonstrate capsules by any of the accepted methods.

Besides the intracellular organisms, there were seen various types of cellular inclusions. Some of the mononuclear cells contained large bodies that stained a deep violet with Giemsa stain. We have seen cells which were filled completely with such bodies (fig. 2). We believe that these represented degenerative stages of the organism, because

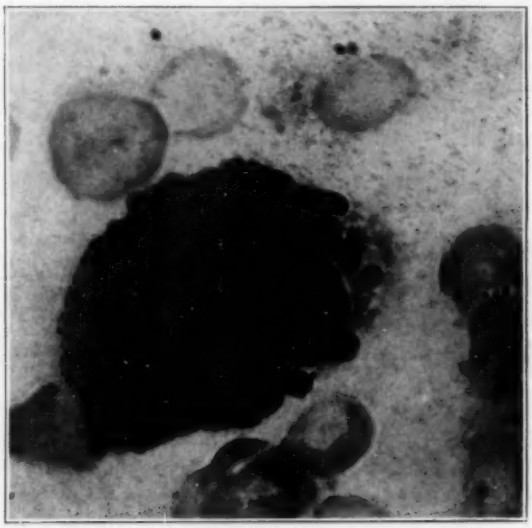

Fig. 2.—Oil immersion photomicrograph of a smear from the lesion showing a mononuclear phagocyte with large inclusions; also extracellular organisms; Giemsa stain.

some forms contained a few granular inclusions. It is certain that they were not nuclear fragments, in spite of identical staining, because the nucleus of these cells was intact even in those that were greatly distended by organisms.

Another type of inclusions appeared as globular bodies within mononuclear cells. These had the forms of homogeneous disks taking a light blue tint with the Giemsa stain. Some of these masses were so large as to occupy a large part of the cell, pushing the nucleus to one side, flattening it, and sometimes causing umbilication.

We believed that the masses described did not bear direct relation to the organisms, but that they were products of cellular metabolism akin to or identical with the so-called plastine masses that occur in the various

diseases. In some cases these plastine masses had been extruded from the cells, leaving large vacuoles.

Still a third type of inclusions were large globular masses that often covered the nucleus like a bonnet and stained a dirty grayish-violet color with Giemsa. These were not homogeneous like the plastine bodies, but granular. In some cases the nucleus was entirely obliterated by these masses. Contours of cocci and bacilli could be distinguished within them. We believed that they represented Zooglear substance produced by the organism and isolating them (the organisms) from the cytoplasm of the cell. The plastine bodies, on the other hand, we believed to be products of cellular metabolism.

HISTOLOGY

Six cases have been examined. In one the appearances were less characteristic, because the section was taken during the stage of healing. In this case there were islands of granulation tissue between dense fibrous strands. In all the other cases the findings were identical.

There was a diffuse cellular infiltration, mainly of plasma cells. Many lymphocytes and connective tissue cells were also found. Numerous mast cells, with metachromatic granules, were seen. The tissue was invaded by numerous newly formed capillary vessels, some of them forming solid endothelial columns and capillary buds. The superficial layers of the granuloma contained a large amount of polymorphonuclear leukocytes. Leukocytes were found, however, in the deepest layers. In spite of the large number of leukocytes, abscesses were not seen. The most characteristic findings were large collections of cells which gave one the impression of honeycomb-like structures. These cells were similar to those described as Mikulicz cells in rhinoscleroma.[11] They had a faintly stained oval, eccentric nucleus; the cytoplasm was either unstained or faintly stained, sometimes showing affinity for basic stains. These cells were filled with micro-organisms, which stained quite well with hematoxylin, but were much better brought out with pyronin methyl green, polychrome methyl blue or Giemsa. In section were seen cocci, diplococci and bacilli. Many of the latter forms showed inclusion bodies (fig. 3).

Further observations on the larger series of cases has forced us to retract the statement in previous papers that the organism took the Gram stain in section. We were unable to demonstrate capsules. There is no doubt that the cells described are identical with those in the smears. The genesis of these cells is not clear. They probably are

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11. Goldzieher, M., and Neuber: Untersuchungen über das Rhinosklerom, Zentralbl. f. Bakteriol. Orig. **51**:2, 1909.

derived from endothelial cells, but a descent from plasma cells in analogy to Mikulicz cells cannot be excluded.

In older cases the tissue contained a varying amount of hyaline connective tissue with islands of plasma cells that showed degenerative changes, gradual loss of basophilic substance in the cytoplasm and a gradual loss of chromatin substance in the nucleus. Due to such changes, cells were formed which had round, faintly stained nuclei and a small amount of poorly stained cytoplasm, forming dendritic processes which made up an intracellular network. Similar unusual degenerative changes of plasma cells have been described by one of us (M. G.)[12] in chronic stages of trachoma.

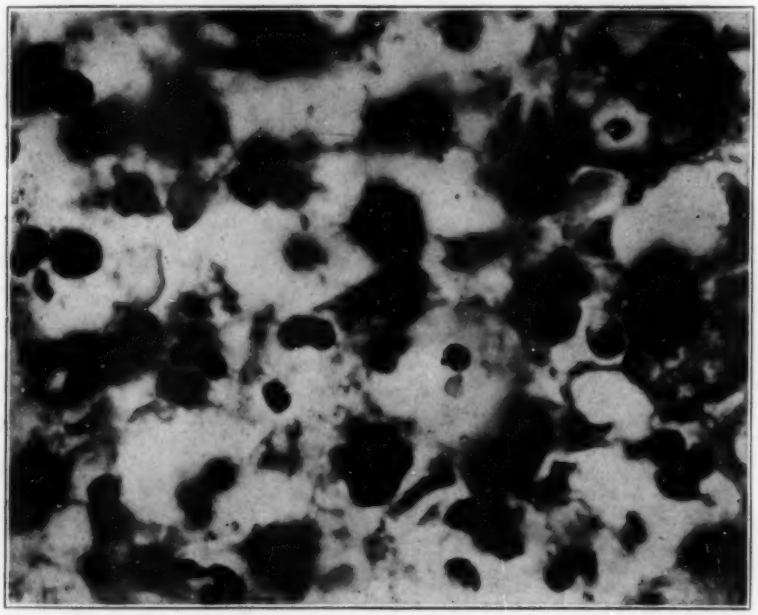

Fig. 3.—Section of venereal granuloma showing large mononuclear cells containing organisms; hematoxylin and eosin stain.

The large arteries in the granulation tissue showed a severe panarteritis not different from that seen in some other chronic inflammations.

The changes of the skin were not specific, but due to the progress of the chronic inflammatory infiltration from below, and eroding the surface. The changes of the papillae were secondary, partly mechanical and partly inflammatory. The epithelium may participate in these secondary changes by marked atypical proliferation. When the lesion went

12. Goldzieher, M.: Die Pathologische Histologie des Trachoma, Verhandl. d. deutsch. path. Gesellsch. **14**:193, 1910.

on to healing, the epithelialization started from the epithelium of the border or from that persisting on the surface, possibly in cutaneous glands or hair bulbs.

BACTERIOLOGY

In five of the seven cases pure cultures of the micro-organisms were obtained. It was easier to obtain cultures from men than from women, because in women the surfaces of the lesions were contaminated by vaginal secretions. The only difficulty consisted in getting the first cultures. Once the organism grew, it easily reproduced itself on subcultures.

The mediums used were broth, agar, ascitic agar, sugar containing agars (Sabouraud's agar) and rabbit blood agar.

BIOLOGIC CHARACTERISTICS

The organism grows best at 37 C., but growth will proceed at room temperature. Growth is most luxuriant under aerobic conditions, but occurs anaerobically.

Sugar Reactions.—Dextrose, galactose, inulin, lactose, maltose and saccharose are acidified with the production of gas. The strains vary in their acid and gas producing qualities.

Hemolysis was absent; no indol production occurred; gelatine was liquefied; milk coagulated, with acid production.

On 4 per cent maltose peptone agar, plate cultures at 37 C., there are seen fine surface colonies in from twenty-four to forty-eight hours. Some strains show no growth until they are forty-eight hours old. All strains reproduce themselves abundantly in twenty-four hours on subculture. On solid mediums there are formed small, round, transparent disks having a bluish opalescence, coalescing in older cultures. The periphery of the colonies is homogeneous, while the center shows a fine granulation. Confluent colonies have a wavy border. In reflected light the colony is gray, but the center of older ones shows a yellowish color and a loss of transparency. The sticky mucoid growth, so characteristic of *B. mucosus,* was not observed. The cultures have a peculiar, sour, fetid odor, like that produced by the lesions.

The growth characteristics on blood agar and rabbit blood agar does not differ from those observed on maltose peptone agar. There is no hemolysis.

Plain and glucose broth become diffusely clouded at the end of from twenty-four to forty-eight hours. Later the growth settles to the bottom of the tube, forming a whitish sediment. In older cultures it assumes a stringy quality and adheres somewhat to the sides of the tube. There is no surface pellicle.

On nutrient and ascitic agar growth differs in no way from that described.

On potato a heavy gray smear is formed, which later becomes brown and colors the edge of the potato black.

The typical forms are best seen in smears from a twenty-four to forty-eight hour growth on Sabouraud's medium. The organisms are from 1 to 6 microns in length; the smallest resemble cocci, diplococci or small bacilli; the larger show a bacillus form that tapers to a point at one end, and contain one, two or three granules (fig. 4). The large bacillus forms which we consider most typical are gram-negative. The smaller forms, especially the coccoid and cocco-bacillus types, are sometimes gram-positive. The inclusion bodies in the large forms are also

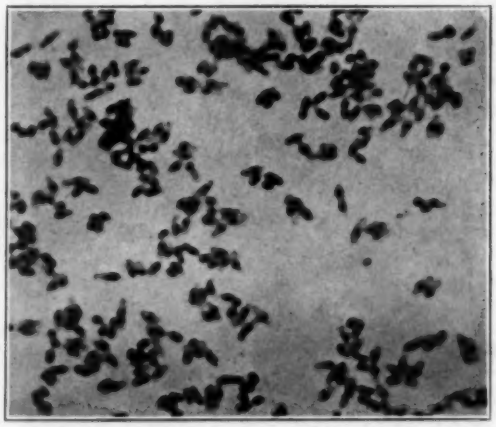

Fig. 4.—Smear of a thirty-six hour culture on Sabouraud's medium; Wright stain.

many times gram-positive. The staining reaction does not depend, as far as we know, on the culture medium; nor could we find any other factor to explain the remarkable pleochromism.

The inclusion granules are different from the so-called polar bodies or any other known intracellular granules. They cannot be stained by special polar body staining methods, such as Abbott's and Moeller's. They do not show metachromatic staining. They are probably intensely stained parts of the bacillar substance, forming two or three round inclusions, often connected with a fine axial thread. Some of the bacilli contain but one coccoid body showing frequently a fine tail-like process. The body of the bacillus is often so faintly stained that it surrounds the darker staining granules like a halo.

In older cultures the swelling of the bacilli progresses and results in the formation of zooglear masses. The faint staining of the bacillus also becomes more marked in contrast to the intense staining of the intracellular granules. The zooglear masses stain with difficulty. Within this zooglea the granules become free and give the impression of cocci (fig. 5).

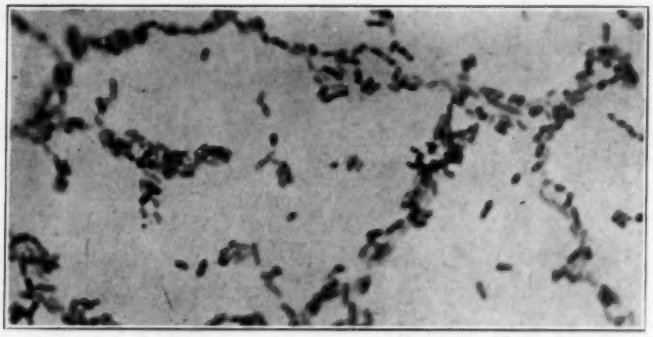

Fig. 5.—Smear of a seventy-two hour culture on Sabouraud's medium; Wright stain.

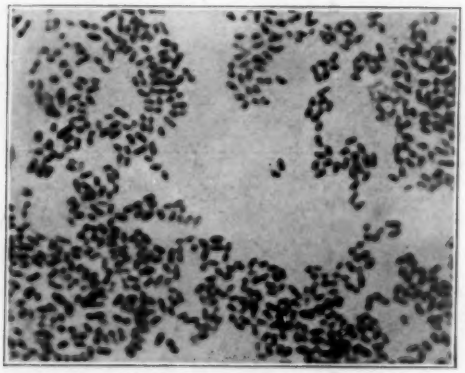

Fig. 6.—Smear of a forty-eight hour culture on lactose agar; Wright stain.

The pleomorphism is surprising, and its various forms seem to bear a relation to the constituents of the medium. Sometimes micrococci are seen, which at first glance appear like staphylococci. More frequently we find a tiny coccobacillus (fig. 6). These forms also show an uneven staining due to the less intense coloration of the margins. Another form often seen is the short chains. This form may contain granules more or less abundantly. In some of the cultures we find large bacilli (fig. 7) the length of which is about three times that of the short form.

It sometimes happens that all the forms described above are found in one culture.

By varying the mediums in early cultures we succeeded in obtaining pure cultures of each of the forms described above. On subculture, or after the culture had become older, another form or the mixed forms appeared again. Further, we saw in old cultures club forms, especially among the long bacilli, suggestive of spore formation. We were unable, however, to demonstrate spores.

The organism never forms capsules either in culture or on the surface of the lesion. We looked for capsules in unstained slides, endeavoring to recognize them by their refractile powers, but without success. All the capsule staining methods tried, such as His, Huntoon, and Buerger, both from culture and in smear from the lesion, failed to show

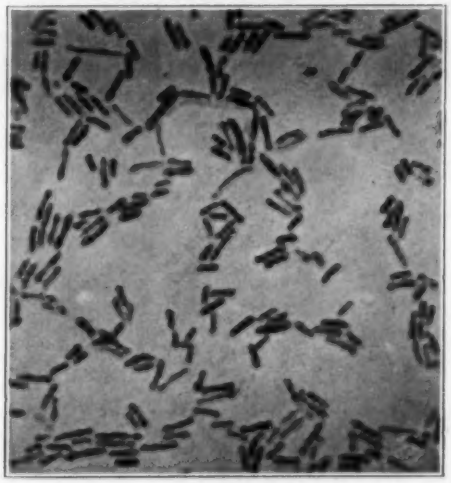

Fig. 7.—Smear of a forty-eight hour culture on dextrose agar; Wright stain.

capsules. We therefore believe that the earlier investigators were mistaken when they ascribed a capsule for the organism. They seemingly misinterpreted the poorly stained or unstained part of the bacillus as a capsule and mistook the coccus-like inclusions for the organism proper. We repeat that the most typical form of the organism is a bacillus in which are coccus-like inclusion bodies. What (fig. 5) others have taken to be a capsule is the proper substance of the bacillus itself. The peculiar appearance may be due to a form of degeneration of the main part of the bacillar substance, undegenerated parts of which, taking a deeper stain, appear like inclusions.

In old cultures smears show less pleomorphism and the organism appears like a small coccobacillus or bacillus. The organism is nonmotile, nonbranching, and does not form spores or pigment.

CHEMICAL ANALYSIS

The cultures have a peculiar smell comparable to that of rancid fat or sour sweat. It was the same as that of the lesion itself. We thought that the smell was due to the presence of a volatile, unsaturated, fatty acid, which we believed might be contained in the zooglear mass. This idea occurred to us when we saw that the zooglea could be removed from the smears by 95 per cent alcohol or xylol, both fat dissolving substances. To identify the nature of the fat, we stained smears with nile blue sulphate. It was found that a large portion of the bacillus consisted of fatty acids which had been stained a dark blue. Other bacilli, stained in the same manner, took but a faint blue stain. If smears of our organisms were first treated with alcohol (95 per cent) no such dark blue stain occurred, because the fatty acid had been removed.

There was a remarkable difference between such cultures and those which had no characteristic odor. The odorless cultures showed the large diffusely staining bacilli with little polar staining or granules. Alcohol did not change this form to any great degree. The cultures, which had the characteristic odor, contained bacilli with distinct polar staining and inclusions (fig. 4). When they were treated with alcohol the bacillus form often disappeared, and the slide showed only small diplococci or coccobacilli. Comparing two slides from the same culture—the one treated with alcohol and the other untreated—it was hardly believable that the two utterly different pictures represented the same organism.

It was stated previously that in older cultures cocci and coccobacilli were seen which were gram-positive. At that time it was not known that as the culture became older the body of the bacillus suffered degeneration. In the gram-stain the alcohol dissolved this degenerated body, freeing the inclusions which often retain the gram stain.

A heavy emulsion of the organism was made from colonies having the characteristic odor. Dr. Cohn, of the United Israel Zion Hospital, found that alcohol, ether and chloroform extracted a substance which when stained with the nile blue sulphate and scharlach R proved to be a mixture of fatty acids and neutral fats. The residuum after the extraction had been made consisted of ordinary bacterial proteins.

ANIMAL EXPERIMENTS

Our results differed in many ways from those of previous observers. The early workers always reported that intraperitoneal injections of their cultures into guinea-pigs or rabbits killed within twenty-four hours. This is characteristic of bacilli belonging to the Friedländer group.

Experiment 1.—A rabbit received intravenous injections with live cultures of the organism in order to obtain an immune serum. Two loops of a twenty-four hour culture, suspended in 1 cc. of saline, were injected. The procedure was repeated five days later. On the twelfth day, three loops of a forty-eight hour culture in 1 cc. of saline were injected. The rabbit showed no systemic effects following the injections, and was killed.

Experiment 2.—Three loops of a forty-eight hour culture, suspended in 1 cc. of saline, were injected intraperitoneally into a rabbit. The animal showed no ill effects during three weeks of observation.

The experiments show a fundamental difference between the behavior of our cultures and those of previous workers. It is hard to explain this, unless we suppose that their cultures were either contaminated with or were really pure cultures of *B. mucosus*. We had much difficulty in isolating our bacillus in the primary cultures because of the much faster growing saprophytic Friedländer's bacillus.

In previous work nodules were obtained in rabbits by intracutaneous injections of broth cultures, and these nodules healed without treatment at the end of five weeks. Cornwall and Peck succeded in isolating the characteristic organism from the lesions in the rabbits, and in reproducing a lesion in another rabbit with reisolation of an organism which was proved to be morphologically and biologically the same.[13]

Sections of the nodules in some cases showed a well walled-off abscess surrounded by granulation tissue, and in others only granulation tissue which in older lesions became densely fibrous. The difference in the tissue reactions was probably due to the difference in amounts of the cultures injected.[9]

The rabbit in experiment 1 had seemingly inadvertently been inoculated intracutaneously in the ear with a small amount of the organism, and in five days it was seen that a nodule about 2 cm. in diameter, capped with a small crust, had developed adjacent to the vein which had been used. During the next two weeks, while the rabbit was receiving intravenous injections into the other ear, it was seen that the nodule rapidly developed and was spreading serpiginously. It was covered with a crust that was rapidly sloughing off. When the rabbit was killed, three weeks after inoculation, the lesion occupied nearly half of the ear surface. The superficial crust was easily removed. The surface of the lesion showed a thin characteristically smelling discharge. The lesion presented a sharply demarcated margin elevated above the

13. Cornwall, L. H., and Peck, S. M.: Three Cases of Granuloma Inguinale with an Investigation Covering the Etiology, Proc. New York Path. Soc., N. S. **25**, nos. 1-5 (Jan.-May) 1925; also footnote 9.

surface, with no undermining. The surface itself was above the skin level and showed the same irregular granulations and hillocks as in the human cases.

On section, the granulations consisted largely of mononuclear cells, with basophilic cytoplasm and eccentric nucleus. They did not show, however, the typical structure of real plasma cells. Scattered about were many polymorphonuclear cells. Some of the large mononuclears contained in their cytoplasm many characteristic pleomorphic organisms. These cells were identical with those in the human lesions. They were found not only in the superficial layers of the granuloma, but could be demonstrated in the subcutis where few leukocytes were encountered.

The appearances described justify the opinion that we have produced a real venereal granuloma in the skin of an animal.

SEROLOGY

Agglutination and complement fixation was tried in four cases. Agglutination was negative for live cultures; in one case, with heated cultures (1 hour at 80 C.), it was positive in 1:200 dilution.

Complement fixation was carried out according to the routine Wassermann technic. We used three different antigens: (1) a bacillus emulsion heated for two hours at 60 C.; (2) an extract of the same emulsion shaken up for forty-eight hours; and (3) the addition of cholesterol to the extract.

Positive complement fixation was obtained in three cases. In one case we obtained a negative result which we attributed to the short duration of the disease. Three normal serums used as a control gave negative results.

An immune serum obtained from a rabbit gave positive complement fixation with the homologous strain up to a dilution of 1:200. This serum will be used in the future to identify new strains of the organism.

As a further proof for the specificity of the organism, we tried allergic reactions and effects of vaccine treatment. The results of these experiments, which will be reported with the clinical paper, were satisfactory enough to maintain our claims.

CONCLUSIONS

Our findings lead us to believe that the organism cultured from granuloma lesions and described above is the etiologic factor in venereal granuloma. The morphology and biology of the organism certainly shows that it is not a protozoon and therefore could not be considered as an "intraepithelial Gregarine" (Donovan body). Furthermore, it certainly shows that it does not belong to the *Bacillus mucosus* group. It differed from all known bacteria by producing fatty acids

There is a slight resemblance in the histology of venereal granuloma to rhinoscleroma, as suggested by Flu.[6] This consists in the presence of Mikulicz cells and in the formation of intracellular bodies. However, in rhinoscleroma hyaline masses are formed in plasma cells, while in granuloma plastine masses are formed. The rhinoscleroma bacillus in tissue section retains the Gram stain and with safranin easily demonstrates a capsule, while in granuloma the specific bacillus does not take the Gram stain, nor does it ever show the capsule with safranin. Even more important is the clinical and anatomic difference between the two diseases. Rhinoscleroma is an extremely chronic lesion of the mucosa which never ulcerates, and which forms firm fibrous tissue as part of its progressive stage, while the venereal granuloma is a serpiginous progressive lesion of the skin which always ulcerates and forms dense fibrous tissue as a feature of its reparative stage only.

SUMMARY

1. Seven cases of granuloma inguinale have been studied.

2. An organism which is biologically and morphologically identical has been observed in all cases.

3. Pure cultures were obtained in five cases.

4. The etiologic agent of venereal granuloma may be called *Bacillus venereogranulomatis*—a proper genus of the family *Bacteriacae*.

5. The venereal granuloma is a cellular granulation tissue showing the specific bacilli in large mononuclear cells.

6. The etiologic rôle of the organism described is supported by the results of complement fixation, allergic tests and animal experiments.

CONGENITAL SARCOMA OF THE TIBIA*

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A great majority of congenital tumors are benign. Among the malignant tumors, three different types can be distinguished. The mixed tumors are the most frequent. These tumors originate simultaneously from two or three of the germinal layers. Next in frequency are the highly differentiated tumors, as for example gliosarcoma. The third and rarest type comprises the true sarcoma and carcinoma.

Alluring as it may be to draw conclusions from malignant congenital tumors as to the rôle of heredity in the etiology of malignant tumors in general, there are no facts to support any such conclusions. A few reported cases in the literature in which a new-born child of a mother with general carcinosis revealed a malignant tumor of the same nature, do not allow any conclusions as to heredity of malignant tumors. Such cases may be explained on the basis of metastases from the mother to the fetus. There is no evidence against the supposition that malignant cells circulating in the blood of the mother might lodge in the body of the fetus. A truly hereditary tumor should not be a metastasis to the fetus but a direct transmission through the germ cells of the parent.

When all sarcomas of the soft tissues are excluded, only five cases of congenital sarcoma originating in or invading the bone are found in the literature, as compiled by Goebel in 1908.[1] Of these five cases, Goebel's case, a periosteal spindle cell sarcoma of the femur in an infant 3 weeks old, is the most interesting because present day methods of treatment were employed—surgical operation combined with irradiation. However, Goebel reported his case about three months after the operation, so that this case cannot be accepted as a cure in the sense of the present knowledge of sarcoma of bone.

REPORT OF A CASE

A girl, 8 weeks old, was admitted to the University Hospital on Oct. 9, 1917, with a tumor of the right leg. The tumor was noticed by the parents at the birth of the patient. During the eight weeks of life, the tumor grew rapidly. On admission, the right leg was about four times as large as the normal left leg. From the roentgenogram, a periosteal involvement of the tibia could be made out. There was a deformity of both bones of the leg, apparently due to pressure of the tumor mass. The clinical diagnosis was

*From the Department of Surgery, University of Iowa.

1. Goebel, Carl: Ueber kongenitalen Femursarkom, geheilt durch Operation und Roentgenbestrahlung nebst Bemerkungen ueber kongenitale maligne Tumoren, Arch. f. klin. Chir. **87**:191, 1908.

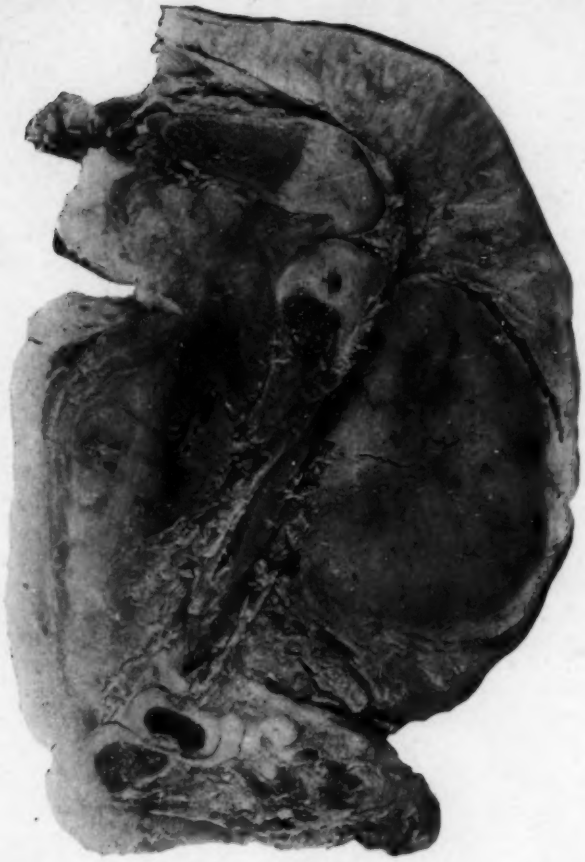

Fig. 1.—Amputated leg of the patient.

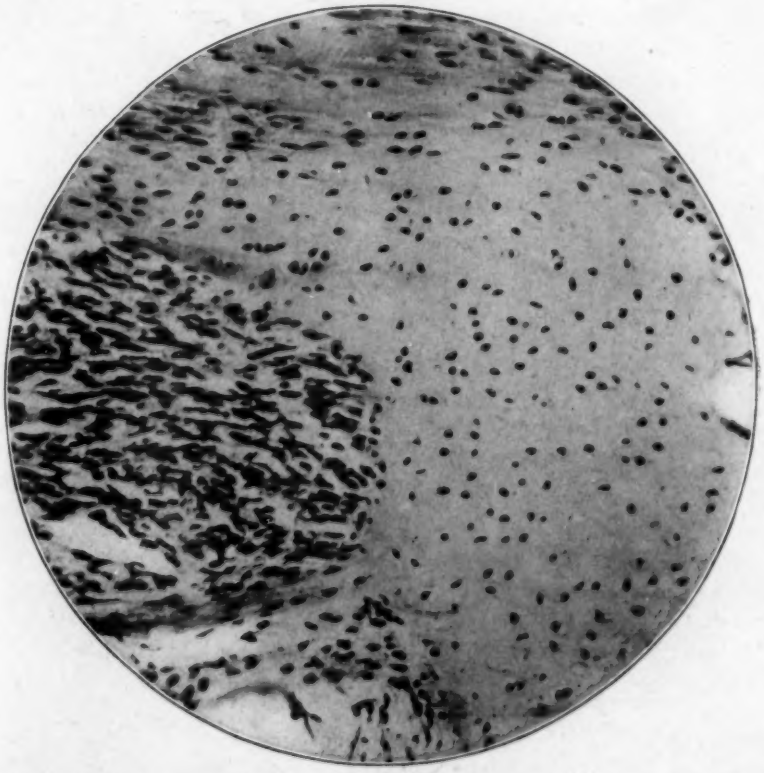

Fig. 2.—Photomicrograph of section through the head of the tibia, showing the invasion of the bone by tumor cells.

"congenital sarcoma of the right leg, probably arising in the bone." A high thigh amputation was made by Dr. Rowan on October 10. At the present time, the patient is 8 years old, well and without evidence of a recurrence or metastases.

An examination of the preserved amputated leg showed that the tumor had replaced practically all of the soft tissues of the leg. Only small remnants of muscle tissue and the tendons were found. The tumor completely surrounded both bones of the leg, filling out the entire interosseous space. On the cut section, the tumor showed a typical fish-flesh firm mass, with areas of necrosis and hemorrhages. Here and there were small cysts lined with a distinct wall and filled with clear amber fluid. These were apparently dilatations of lymph vessels as a result of pressure disturbances in the lymph flow.

Sections taken from the periphery of the tumor showed a typical round cell sarcoma with a perithelial arrangement. The cells become more and more differentiated the closer to the tibia the sections were taken. The round cells change into spindle cells with occasional hyalinization and formation of osteoid tissue. Sections passing through the head of the tibia showed a distinct invasion of the bone by the tumor. This type of bone sarcoma — periosteal fibrosarcoma — is known to give a fair prognosis after radical operation as compared with other types of sarcoma of bone.

FAMILIAL JUVENILE CIRRHOSIS OF THE LIVER*

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While many cases of juvenile cirrhosis have been reported, there seems to be no general understanding with regard to their classification. Some of the reported cases were definitely of congenital nature, due partly to syphilis and partly to bile duct anomalies resulting from either formative or inflammatory disturbances. Cases of juvenile cirrhosis of probable congenital origin based neither on syphilis nor on anomalies of the bile ducts seem to be exceedingly rare. The opportunity to study a case that apparently belongs in the last named group has furnished the occasion for a review of the question of juvenile cirrhosis. While the available literature has not permitted an exhaustive study, it has been attempted to ascertain from the descriptions at hand the general notions as to etiology and pathologic changes and to undertake a grouping of the material from one or the other of these standpoints.

In 1887, Howard[1] collected from the literature sixty-one cases of cirrhosis of the liver in children up to the age of puberty, exclusive of those due to congenital defects of the bile ducts, and added two of his own. He found that in only ten of these cases did the cirrhosis of the liver occur in persons under 3½ years of age. Of the more clearly established etiologic factors, he finds that alcohol occupies the uppermost rank and is held responsible for 15 per cent of the cases; syphilis, for 11 per cent; tuberculous disease of other organs than the liver, for 11 per cent. Less frequent conditions are "venous congestion of the liver, peritonitis, and a general tendency to connective tissue formation in the system." In more than half of his sixty-one collected cases nothing definite could be ascertained with regard to etiology; likewise in his own two cases of cirrhosis, occurring in a 9 year old girl and, six years later, in her brother at 8 years of age. The anatomic changes in the liver and the secondary functional disturbances did not seem to vary from those of adults. Of Howard's collection of sixty-three cases, fifty-six were nonsyphilitic. Of these (fifty-six), nineteen cases showed changes in the liver conforming to those of atrophic and thirteen to those of hypertrophic cirrhosis. Thirty-four cases of the same group were associated with ascites and twenty-three with jaundice.

*From the Department of Laboratories, Buffalo General Hospital, Buffalo, N. Y.

1. Howard, Palmer: Am. J. M. Sc. **94**:350, 1887.

Of the congenital type of cirrhosis not due to syphilis, we have the first large collection of cases by Thomson.[2] This author tabulated forty-nine cases from the literature and added one of his own, forming a group in which the cirrhosis apparently was due to anomalies of the bile ducts. The anomalies consisted either of faulty development in the form of absence or "atresia" (Lavenson[3]) of the ducts, or to obstruction from without or within, as a result of anomalies or inflammatory changes. In many cases the question as to the primary (truly developmental) or secondary nature of these anomalies is doubtful.

Later comprehensive reviews of this type of cirrhosis include those of Benecke,[4] Howard and Wolbach,[5] and Holmes,[6] bringing the total number of recorded cases up to 114. Howard and Wolbach divided the cases into four classes based on the location of the obliteration. Holmes published a complete list of the cases reported up to that date, with diagrams of all the types of anomalies found. He extended the classification to six definite groups, comprising all the anomalies that have occurred in the extrahepatic bile ducts. Whether the addition of a seventh group consisting of intrahepatic bile duct obstruction associated with biliary cirrhosis, as suggested by Gordon,[7] is justified, seems questionable.

While there is no question as to the absence of syphilis in the later cases of the foregoing group, some doubt may be entertained as to the earlier cases. However, the exact number of clear-cut, nonsyphilitic cases of cirrhosis associated with bile duct anomalies is irrelevant, as the existence of such a group independent of syphilis appears definitely established.

The form of cirrhosis in these cases is usually described as hypertrophic biliary cirrhosis with histologic pictures characteristic of this type in adults. It is invariably associated with jaundice but hardly ever with ascites.

It may be important to emphasize the general tendency of juvenile cirrhosis to run in families, even if we exclude cases due to syphilis or to congenital anomalies. One illustration of this tendency has already been seen in the two cases of Howard. As further examples may be cited the cases of Jollye[8] and Ely.[9] In 1892 Jollye reported two cases of cirrhosis of the liver, that of a boy aged 11 and that of his sister

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2. Thomson, J.: Edinburgh M. J. **37**:523, 604, 724, 1891-1892.
3. Lavenson, R. S.: J. M. Res. **18**:61, 1908.
4. Benecke, cited by Holmes: Am. J. Dis. Child. **11**:405, 1916.
5. Howard and Wolbach: Arch. Int. Med. **8**:557, 1911.
6. Holmes, J. B.: Am. J. Dis. Child. **11**:405, 1916
7. Gordon, K.: Boston M. & S. J. **187**:923, 1922.
8. Jollye, F. W.: Brit. M. J. **1**:858, 1892.
9. Ely, Theodore: Boston M. & S. J. **170**:542, 1914.

aged 10. In these cases, however, both children had developed a remarkable liking for vinegar, of which they habitually partook in considerable quantities. Both children had had measles, but nothing else that might come into consideration as an etiologic factor was discoverable. Ely's cases occurred in twin boys, aged 4, with a history of measles in both. From the age of 14 months, these children had received considerable quantities of brandy. One of them was examined postmortem, and the liver was found to be the seat of a cicatricial atrophic cirrhosis. Associated with this was a generalized miliary tuberculosis. Ely attributes the cirrhosis to the alcohol, although, according to the pathologist (Karsner), there was no anatomic support for this opinion.

The familial tendency is also clear in certain cases of progressive lenticular degeneration associated with hepatic cirrhosis as first described by Wilson [10] in 1912, and otherwise known as Wilson's disease. This cirrhosis is usually the atrophic type, associated with ascites and without jaundice (Wilson; Howard and Royce [11]).

Another large series of juvenile cirrhosis with outspoken familial tendency is the so-called Indian cirrhosis. This disease has been studied especially by Gibbons,[12] by MacKenzie [13] and by Ghose.[14] The last named author has collected 400 such cases. The disease occurs in infants between 6 months and 3 years of age in certain districts in India, but probably also in Mexico. The pathologic changes in this form of cirrhosis were described by Gibbons in 1888. Mukherjee [15] regards the disease as the result of dietary errors; Abt,[16] taking cognizance of the frequent febrile crises, suggests an infectious basis; others consider the etiology as obscure.

Pathologically this is sometimes described as Hanot's hypertrophic cirrhosis. Mukherjee states that the initial process is first an intercellular fibrosis which later extends to the portal sheaths and interlobular areas. This hypertrophic stage is followed by a stage of contraction in which the liver becomes rapidly smaller, and finally by a stage of regeneration during which the new liver is formed, as in the embryo, by the new-formation of masses of liver cells from the proliferation of bile ducts. The picture found at necropsy varies greatly, depending on whether the subject dies early from intercurrent disease or later when

10. Wilson, S. A. K.: Oxford Medicine, 1921 ed., section on Diseases of the Basal Ganglia.

11. Howard and Royce: Arch. Int. Med. **24**:499, 1919.

12. Gibbons, J. B.: Internat. M. Ann., 1891, p. 323; cited by Morse: Boston M. & S. J. **147**:299, 1902.

13. MacKenzie: Lancet **1**:322, 1895.

14. Ghose: Lancet **1**:321, 1895.

15. Mukherjee, S. K.: Ind. M. Rec. **41**:273, 1921; **42**:11 and 79, 1922.

16. Abt, I. A.: Med. Clin. N. Amer. **3**:13, 1919.

the reparative process has proceeded to a considerable degree. The spleen is usually enlarged; jaundice is present early and ascites later.

From the foregoing, it may, perhaps be seen that there are no special features in juvenile cirrhosis which would distinguish it from the usual run of cases of adult cirrhosis. With regard to etiology, we encounter theories for acquired cases identical with those in adults (alcohol, infectious diseases, gastro-intestinal intoxication, etc.), and the same is true of the pathologic anatomic changes in the liver and of the secondary phenomena. In the congenital (nonsyphilitic) variety, in which bile duct obstruction or atresia is a prominent feature, we also find a type of cirrhosis analogous to the cirrhosis of adults resulting from similar causes, namely, biliary cirrhosis.

Furthermore, we find in children a type of cirrhosis resulting from chronic congestion, especially in cases of heart disease, corresponding to the so-called "cirrhose cardiaque" of French authors as exemplified in the cases of Hutinel,[17] Hanot,[18] and Parmentier.[19]

Then there is a definite group of cases of juvenile cirrhosis which may be said to resemble that group of adult cirrhosis which has recently been separated, especially by Eppinger,[20] from the large group of hepato-lienal diseases (Naunyn [21]) as splenomegalic cirrhosis. In this group are included those cases of cirrhosis in which the most prominent feature, at least in the beginning, is rather the enlargement of the spleen than the changes in the liver, which usually manifest themselves toward the end of the disease. The clinical picture at the outset is variously designated as splenic anemia or Banti's disease. Perhaps the best illustration of such a cirrhosis is afforded by the second case of Hanau,[22] although this author includes all four of his cases in this group. But there are undoubtedly many other illustrations of so-called Banti's disease in young persons whose disease must have existed since infancy.

The case forming the subject of this report seems to fit best from a clinical standpoint, at least, in this group.

REPORT OF A CASE

History.—M. M., a girl, aged 4, of Scottish parentage, was admitted to the Buffalo General Hospital on July 9, 1925, with the history from her parents that she had gradually lost weight and strength for the past year, and that her abdomen had been slowly increasing in size for about the same time.

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17. Hutinel, cited by Morse: Boston M. & S. J. **147**:299, 1902.
18. Hanot, cited by Morse: Boston M. & S. J. **147**:299, 1902.
19. Parmentier, cited by Morse: Boston M. & S. J. **147**:299, 1902.
20. Eppinger, H.: Enzyklop. d. klin. Med., 1920, section on hepato-lienal diseases.
21. Naunyn, cited by Hanau: Monatschr. f. Kinderh. **29**:54, 1924-1925.
22. Hanau, F.: Monatschr. f. Kinderh. **29**:54, 1924-1925.

For the first year of her life apparently she had been well. At the end of her first year the abdomen became distinctly large, but she was otherwise "healthy," corresponding mentally and physically with a normal child of her age. At the end of the third year, a circumscribed swelling in the upper part of the abdomen was noticed by the parents, which slowly became more prominent. The child became pale and thin and gradually lost strength until the time of her first entrance into the hospital. There was no history of hemorrhages before entrance.

The father had always been well and strong. The mother's history yielded nothing except that she had had scarlet fever at 10 years of age; she was

Fig. 1.—Section from liver, showing relation of parenchyma to stroma; low power magnification.

now 29. The grandparents on both sides were alive and in good health. There was no knowledge of any condition similar to this in any member of either family.

The mother had given birth to three children, the first a boy, who from the age of 9 months had had an increasingly swollen abdomen, and who died at the age of 4½ years. The second child was the patient. The third child, aged 4 months, had had hemorrhages from the mucous membranes on the

second and third days of life, was successfully treated with serum, and was now apparently well.

The first child[23] first came under the observation of Dr. Findlay in the Royal Hospital for Sick Children in Glasgow on March 10, 1921, at the age of 2½ years, with the history of having had a steadily increasing swelling of the abdomen from the age of 9 months. On examination the abdomen was found to be swollen and the liver palpable one fingerbreadth below the costal margin; it felt hard and had an irregular surface. The spleen was also felt one fingerbreadth below the costal margin. Otherwise the physical examination was negative. The provisional diagnosis was cirrhosis of the liver.

Fig. 2.—Section from liver, showing a connective tissue band with numerous new bile ducts especially along the periphery of the liver cell islands.

The patient again came under the observation of Dr. Findlay on Nov. 18, 1922, with a history that he had improved somewhat after his first visit and that the spleen, according to the family physician, had diminished in size. Later, however, he had become very much worse, paler, weaker, and had looseness of the bowels. On admission he was very pale, showed clubbing of the fingers, enlargement of the heart and a systolic murmur. The liver was one

23. I am indebted to Dr. L. Findlay for his communication containing these notes.

and the spleen four fingerbreadths below the costal margin. The blood examination showed the hemoglobin to be 30 per cent; red blood cells, 1,980,000; white blood cells, 9,200. The smears showed nothing abnormal. The Wassermann reaction was negative. The patient remained in the hospital for three and one-half weeks, during which time there was constant fever, slight diminution in the size of the spleen, and increase in that of the liver. Blood culture was negative. On this occasion it was felt that it might be a case of Banti's disease.

Physical Examination of Our Patient.—Weight on admission was 32 pounds (14.5 Kg.). On superficial inspection the child was apparently not very sick,

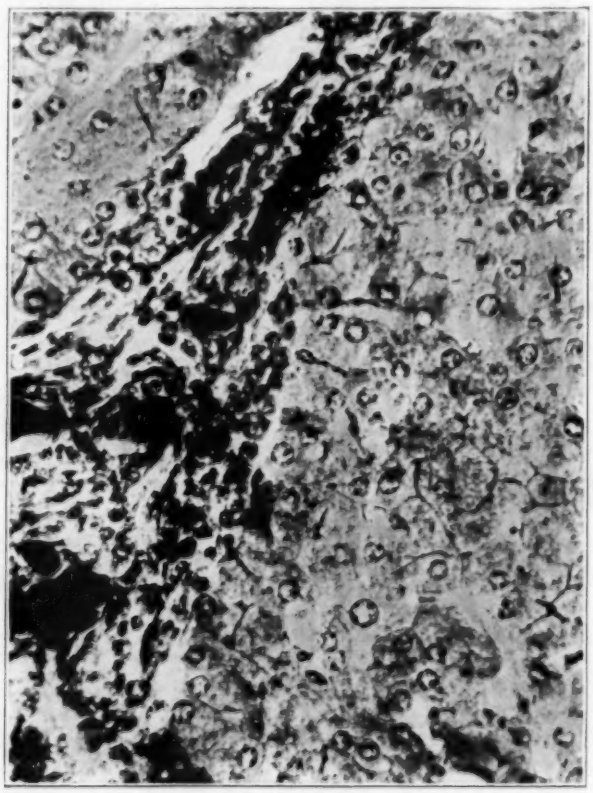

Fig. 3.—Section from liver. Bile capillary stain, showing intercellular and intracellular bile capillaries as in normal liver cells.

rather pale and the extremities thin; the trunk showed a general barrel-shaped enlargement. The superficial veins over the chest and abdomen were clearly visible but not greatly distended. There was a brownish discoloration on the back of the neck but no signs of hemorrhages anywhere.

On palpation the liver was found to be markedly enlarged, especially on the left side, filling in the subcostal angle. The spleen was even more prominent, occupying the entire left upper quadrant of the abdomen and its lower pole at the level of the umbilicus.

The temperature was normal, the pulse rapid. Examination of the blood showed: hemoglobin 60 per cent (Sahli); red blood cells, 2,896,000; white blood cells, 5,800. The differential count showed nothing abnormal. The bleeding as well as the clotting time was normal; the Wassermann reaction was negative. Wassermann examinations of the blood in both of the parents and in the four months' old baby were negative. The urine showed regularly a more or less heavy trace of albumin and a few hyaline and granular casts. Tests for urobilin were negative.

Diagnosis.—With the enlargement of the spleen as the most prominent feature of the case and in the presence of the blood findings ruling out a leukemic condition though not the possibility of an aleukemia which must always be reservedly borne in mind in all such cases, such possibilities as Hodgkin's disease, Gaucher's disease and Banti's disease, in the wider sense of the word, were to be taken into consideration. However, in the presence of the low white count with no relative increase in the polymorphonuclear cells, with no lymph-node enlargement and no marked rise in temperature, Hodgkin's disease could not seriously to be entertained as a diagnosis in this case. On the other hand, with the definite evidence of a similar disease having affected another member of the family, a tentative diagnosis of Gaucher's disease seemed more acceptable, particularly since at that time neither jaundice nor ascites nor any symptoms with reference to a congestion of the gastro-intestinal tract were demonstrable.

Course of Illness.—A profuse epistaxis occurred on July 27, the first hemorrhage that had occurred. Three days later, the mother noticed that the child was very pale. On that day, arising suddenly from sleeping, the child vomited dark coffee-ground material immediately followed by an emesis of bright red blood. A few hours later she was brought to the hospital.

Second Admission.—On second admission the patient was extremely pale; the pulse rate was 140; temperature, normal; blood pressure, 60 systolic and 10 diastolic; hemoglobin, 30 per cent (Sahli); red blood cells, 2,100,000; white blood cells, 4,800; benzidine test of the stool for occult blood, +++. The Wassermann test of the blood was repeated and was again negative.

The liver seemed larger than on previous examinations, and evidence was present of a small amount of fluid in the abdomen.

The spleen which had been markedly enlarged during the first stay in the hospital now seemed considerably reduced in size, and during the last two weeks its mass diminished until it disappeared under the costal margin.

On August 9 a blood emesis occurred. The abdominal fluid had been progressively increasing in amount, and on August 10 the abdomen was tapped and a liter of clear yellow fluid removed. During the next few days the patient became gradually weaker, the heart showed evidence of exhaustion, the respiratory rate increased and with a terminal rise in temperature and onset of coma, she died on August 21.

With the advent of hemorrhages and ascites the assumption that the patient was suffering from some form of cirrhosis of the liver seemed more plausible, yet the familial element in the case, on the one hand, and the absence of any trace of jaundice, on the other hand, seemed to justify the suspicion of Gaucher's disease.

Necropsy (restricted to abdominal incision).—Anatomic Findings (Dr. Roman): The cadaver was that of a female child, 103 cm. in length, of tender skeletal structure, with body heat partly retained, beginning rigor mortis in the lower extremities, and no livores anywhere.

The skin was pale gray, with a few dilated veins over the chest, but none on the abdomen. The hair was blond, the visible mucuous membranes pale, the pupils equal and moderately dilated. The neck was long, the abdomen and chest were in proportion, the lower extremities edematous; there was slight edema of the hands.

In the abdomen there was a considerable quantity of clear fluid; the serosa was smooth everywhere, but slightly thickened in places.

The diaphragm on the right side was at the lower border of the third rib; on the left side, in the third intercostal space.

The left lung was closely adherent to the chest wall in a few places; the right lung was free; in each pleural cavity there was a slight amount of clear fluid; in the pericardium, about 30 cc. of similar fluid.

The mucous membrane of the esophagus was pale. The bronchial lymph nodes were somewhat enlarged, especially the lower tracheobronchial ones. The mucous membrane of the trachea and bronchi was pale.

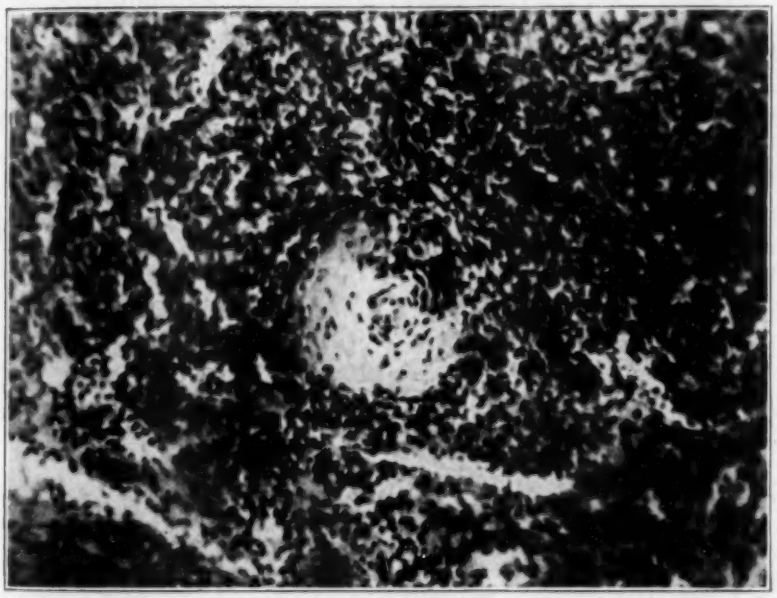

Fig. 4.—Section of spleen showing central fibrosis in one of the follicles (fibro-adenitis, Banti); hematoxylin and eosin stain.

The epicardium showed many pin-point hemorrhages, and on the anterior surface of the right ventricle, a bandlike tendinous thickening.

The heart valves appeared intact and tender everywhere. Through the foramen ovale an ordinary probe could be passed with ease. The heart was uniformly enlarged; the heart muscle showed through the endocardial lining exquisite tiger-skin markings. The left ventricle appeared dilated; the heart apex was obliterated.

The spleen weighed 180 Gm. and showed multiple, rather deep, notchings in its anterior border. The capsule was generally thin, with numerous grayish flecks; its consistency was considerably increased. The cut surface was dark grayish red, showing prominently thickened trabeculae, but hardly any

follicles. The vessels, as far as they could be viewed grossly, showed nothing remarkable.

The liver weighed 720 Gm. Its capsule was smooth, except at the middle of the lower surface where it was thickened in patches. One of these patches seemed to have constricted a portion of liver tissue into a pendulous lobule of about the size of a hazelnut. The consistency was very much increased, being cut with difficulty, and the cut surface showed entirely irregular markings. The acinar markings seemed to be replaced by larger but irregular lobules embedded in a pinkish-gray vascular stroma. The entire liver was intensely jaundiced.

The gallbladder was filled with normal looking bile; the large bile ducts were present and free from obstruction as far as they could be traced. In the liver substance their ramifications were surrounded by markedly increased

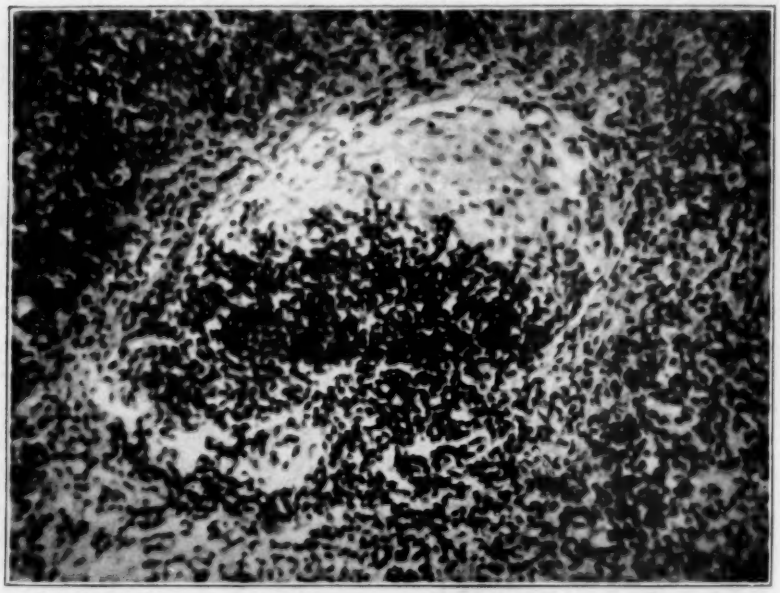

Fig. 5.—Section of spleen showing peripheral fibrosis in one of the follicles; hematoxylin and eosin stain.

stroma. The portal vein, the splenic and mesenteric veins, the hepatic artery were all normally located and showed no remarkable changes.

In the gastro-intestinal tract there were no abnormal contents; the mucosa of the stomach was hyperemic.

The kidneys together weighed 160 gm. They, as well as the rest of the organs of the genito-urinary tract, showed no remarkable changes.

Anatomic Diagnosis.—The diagnosis was: cirrhosis of the liver with moderate ascites and moderate enlargement of the spleen; high-grade anemia of the organs; fatty degeneration and dilatation of the heart.

Microscopic Findings.—Sections from various parts of the liver showed the same pictures. Nowhere was normal liver structure discernible, nowhere were typical acini to be found. The whole liver consisted of an irregular network of bands of liver parenchyma embedded in dense connective tissue. The pro-

portion of these two tissues roughly estimated was about equal. While the bands of parenchyma appeared to be a continuous network in most places, in others they were interrupted, the fibrous tissue cutting, as it were, into the bands of liver cells, constricting many portions into irregular, roundish or oval nodules or completely severing such from their union with the rest; but nowhere was connective tissue to be found isolating single elements from their connection.

The cells making up the parenchyma differed little from normal liver cells, except that in the central parts of the bands or islands the cytoplasm was considerably vacuolated; the vacuoles, however, contained no fat (sudan III stain on frozen sections). With specific stains for bile capillaries (Vance's method) the latter were demonstrable in many places as in normal liver cells in the periphery of the cell bands, but rarely in the center. In no instance did they seem dilated. The distribution of capillaries and Kupffer cells seemed

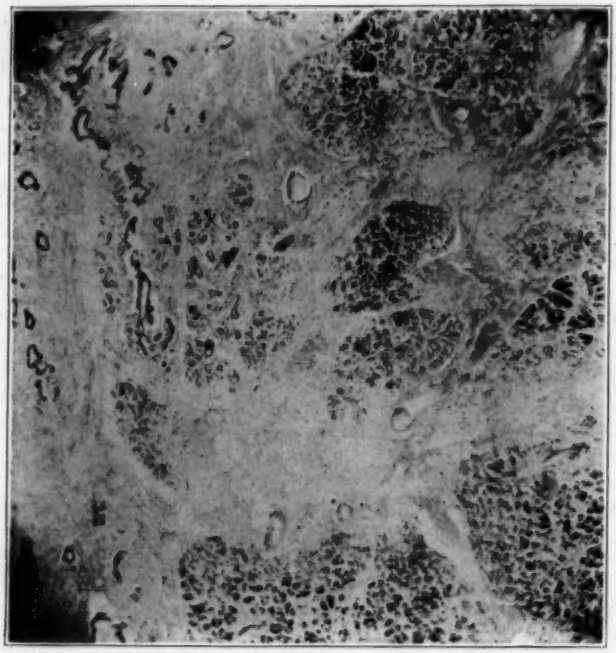

Fig. 6.—Section of pancreas; diffuse fibrosis, regeneration of ducts and postmortem necrosis; low power magnification.

normal throughout. The vessels showed a rather marked dilatation toward the periphery. Larger blood vessels in the shape of central veins were present but irregularly placed, and were occasionally to be seen cutting into the bands from the surrounding stroma.

The connective tissue making up the framework for the liver parenchyma was fairly well supplied with fibroblast nuclei in most places; in others, it was poorly nucleated and hyalinzed. Round cell infiltration was rarely to be seen in a few places. The larger blood vessels carried by this tissue, veins as well as arteries, showed considerable thickness of their walls. The capillaries were numerous, and many dilated lymph spaces were noticeable. However, the most prominent content of the connective tissue stroma was the enormous

number of young bile ducts in all stages of development. In most instances they consisted of cords of bile duct epithelium without lumina; in others they were distinctly canalized, and in many places they seemed to be distended to the utmost with bile thrombi. This distention of the bile ducts was prevalent throughout, and was obviously responsible for the icteric color of the liver. Nowhere were the liver cells stained with bile pigment.

In those parts of the stroma which were adjacent to the liver cell strands, bile-duct proliferation was particularly marked. Here one could actually trace the transition of bile duct epithelium into liver cells and observe the communication of the bile capillaries of the latter with the small biliary radicles.

The general architecture of the spleen was preserved, but the entire fibrous framework was uniformly and markedly increased, as was evidenced by ordinary stains from the thickening of the capsule of the trabeculae and the enormous amount of fibrous tissue in the pulp. The follicles were very small and invaded by coarse connective tissue. The overgrowth of connective tissue in the spleen was particularly well demonstrated with Mallory's connective tissue stain (Zenker fixation), the fibrosis of the follicles thus especially coming to view in the form of considerable thickening of the reticulum which in places appeared to have brought about the disappearance of the lymphocytes.

With regard to the cells making up the parenchyma of the spleen, those of the follicles, or what was left of them, were true to type—small lymphocytes. Germinal centers were nowhere to be found in them. The cellular part of the pulp seemed to be made up mostly of myeloid elements, and, with the exception of megacaryocytes and fat cells, the pictures were often very much like those of bone marrow, neutrophilic myelocytes and large hematoblasts being especially prominent. A similar condition prevailed in the several mesenteric lymph nodes that were examined. Here, however, fibrosis was not prominent, except to a slight degree, in the form of a thickening of the reticulum of the marginal follicles. The sinuses appeared dilated everywhere, filled with macrophages and lymphocytes; while everywhere around the vessels, foci of myeloid cells, as in the spleen, were to be found.

Sections from the pancreas showed, besides postmortem necrosis, a high-grade interstitial fibrosis, affecting both the interlobular and interacinous connective tissue. Very much as in the liver, the connective tissue was only moderately well nucleated, showed practically no round cell infiltration, and numerous variously sized and shaped young ducts. The process of fibrosis occasionally involved the islands of Langerhans.

The only marked histologic change in the heart was a high-grade fatty degeneration of the muscle cells affecting the organ diffusely, but more especially in alternating layers.

In the kidneys, there was granular degeneration of the parenchyma but no interstitial or vascular changes.

COMMENT

Reviewing the pathologic findings of the case, it will be seen that the most prominent changes are represented by a cirrhosis of the liver which, according to current conceptions, in spite of the comparatively large size of the organ, will be designated as atrophic cirrhosis. In consonance with this stands the ascites and the absence of jaundice and probably also the sclerosis of the pancreas. Even the size of the spleen as it was found at necropsy would harmonize perfectly in its gross appearance with this

form of cirrhosis. Nor is the high-grade fibrosis of the organ contradictory to a long standing cirrhosis of this type.

The myeloid metaplasia of the spleen can hardly be looked on as an independent process, indicating possibly a leukemic hyperplasia, since the case showed a high grade of anemia. Myeloid metaplasia is well known to accompany anemias in general (Naegeli [24]), and is particularly prevalent in childhood. It is, therefore, safe to assume that the myelogenous transformation seen in the splenic pulp as well as in the lymph nodes is entirely a secondary process.

Nevertheless, there is enough clinical evidence to indicate that the spleen had for a long time been considerably larger and, in fact, was the most prominent feature of the disease. The same is true of the patient's brother. In the absence, however, of the changes characteristic of Gaucher's disease in any of the organs examined, and in the presence of the cirrhosis, no other interpretation seems permissible than that the enlargement of the spleen, regardless of the extent, is in connection with the cirrhosis.

Thus, if we are to take the course of events in the patient's illness, and not only the anatomic findings, into consideration, we must classify the disease with that group which manifests itself primarily with splenic enlargement. In these cases, the cirrhosis of the liver does not become apparent until later, regardless of whether it has started simultaneously with, preceded or superseded, the splenomegaly. This group has already been referred to above as splenic anemia, often in this country used synonymously with Banti's disease.

Banti's disease as described by Banti,[25] as a clinical and pathologic entity, is far from being universally accepted. The so-called fibro-adenitis of the spleen beginning in the centers of the follicles, which Banti claimed as specific for this disease, is said to occur in other forms of chronic enlargement of the spleen (Marchand [26] and others), but even those who do not deny the existence of a Banti's disease (Eppinger) emphasize the great rarity of it outside of Italy. Furthermore, although Banti's disease has been described in early life (Finkelstein [27]), our patient was entirely too young, and above all did not show the blood picture held by Banti and his supporters to be characteristic of the disease.

It is, nevertheless, of interest to note that the histologic pictures of the spleen in the case under discussion, as demonstrated by Mallory's stain, reveal a central fibro-adenitis quite analogous to the pictures

24. Naegeli, O.: Blutkrankheiten und Blutdiagnose, 1912, pp. 254, 261.
25. Banti, cited by Eppinger: Beitr. z. path. Anat. u. Path. **24**:21, 1898.
26. Marchand, cited by Eppinger, footnote 20.
27. Finkelstein, cited by Eppinger, footnote 20.

figured by Eppinger from Banti's original specimens. On the other hand, pictures were seen from the same spleen which are analogous to the pictures figured by the same author as fibro-adenitis not characteristic of Banti's disease.

The adherents to the theory that Banti's disease is a definite entity regard many of the cases that have been described in the literature as not well founded, and because of the great prominence of the splenic enlargement in such cases, speak of them in the sense of Eppinger as splenomegalic cirrhosis. The basis for this new name is the idea that in this form of cirrhosis the associated affection of the spleen is not necessarily dependent on that of the liver. The spleen is assumed to have a certain autonomy, although coordinate with the liver, in the development of its changes, and the changes may, under certain circumstances, exceed those of the liver. It seems that more proof of the correctness of this theory would be necessary than is offered. This consists in the observations of the favorable effect of splenectomy on some of the symptoms. Ranzi [28] reports fourteen such cases with splenectomy. Of these, four have shown improvement, five and one-half years, two years, eight years, and two months after the operation, respectively. On the other hand, two cases one and one-half years and one year after the operation, respectively, showed no improvement. Of the rest, two died at the operation and the remainder of intercurrent diseases.

At any rate, our case with the marked splenomegaly during the course of the disease may be appropriately designated as splenomegalic cirrhosis whether or not the separation of such a group is well founded. Reports of just such cases of juvenile cirrhosis seem to be scarce in the literature. Yet there are probably more analogous cases reported than the one of Hanau alluded to above. Even that case differed somewhat from ours, as the patient exhibited jaundice during the first three months of life. A case recently reported by Schuscik [29] may also be mentioned in connection with this. In that case (a girl, aged 2) the spleen was markedly enlarged at necropsy and showed approximately similar changes. However, there was definite jaundice, and the changes in the liver seemed to be in the nature of a hypertrophic cirrhosis.

Regarding the time of origin of the disease in the case presented, although symptoms did not appear until the end of the first year, the disease obviously started at an earlier date. It is, of course, possible that both children had acquired their cirrhosis very early in life, perhaps as a result of the same environmental or dietary influences. On the other hand, the familial element would seem to point to the congenital nature of the disease, at least to an inherited vulnerability of the liver.

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28. Ranzi, E.: Enzyklop. d. klin. Med., 1920, section on hepatolienal diseases.
29. Schuscik, O.: Arch. f. Kinderh. **68**:144, 1920-1921.

SUMMARY

A case of cirrhosis of the liver is presented in a 4 year old girl, who, during her illness, because of a marked enlargement of the spleen presented a picture of some form of splenic anemia. Necropsy revealed atrophic cirrhosis of the liver, cirrhosis of the pancreas and histologic changes in the spleen of the nature of a diffuse fibrosis and fibroadenitis of the follicles as described by Banti for Banti's disease. Besides this, a high-grade myeloid metaplasia was found in the spleen and lymph nodes, which is assumed to be of secondary nature. A brother of this child had exhibited the same clinical picture, and had died at about the same age, three years ago.

From a study of the literature, juvenile cirrhosis does not seem to differ essentially from adult cirrhosis, as the same pathologic varieties are encountered. The cases reported may be roughly divided into (*a*) acquired cirrhosis and (*b*) congenital cirrhosis. Besides being associated with syphilis, congenital cirrhosis is usually associated with anomalies of the bile ducts. There is a small group of cases which may be said to correspond to that type of adult cirrhosis which is often loosely spoken of as Banti's disease or as splenomegalic cirrhosis. With this group the case presented is classified.

There is a striking tendency for juvenile cirrhosis to occur in more than one member of the same family, as seen especially in Wilson's disease and in the Indian-Mexican cirrhosis.

SIMULTANEOUS OCCURRENCE OF CARCINOMA AND TUBERCULOSIS OF THE UTERUS*

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The infrequency of the association of carcinoma and tuberculosis has been noted repeatedly. The first observation is credited to Rokitansky,[1] who stated that carcinoma and tuberculosis occur together only in rare instances, and that this is true even of the relative localization of the two processes in the same organ. For example, the vaginal and cervical portions of the uterus are usually susceptible to carcinomatous change, while the endometrium of the corpus is more often tuberculous. McCaskey[2] felt that Rokitansky was not so definite in his assertions as subsequent quotations would have us believe.

Nevertheless, the simultaneous occurrence of the two processes has been observed not only in the same organism, but also in the same organ. White[3] has reported the association in 12 per cent of 180 necropsies, considering only tuberculosis if it were recent and active. Other statistical observations are in agreement. It is obvious that from a purely statistical standpoint the idea of mutual exclusion is untenable.

Observations have been made and recorded with a fair degree of frequency concerning the occurrence in the same organ, but much more rarely than the occurrence in the same organism. "Cancroid" has developed in a tuberculous cavity of the lung (Friedländer,[4] Schwalbe[5]). The combination of carcinoma and tuberculosis has been encountered in the esophagus and larynx (Pepper and Edsall,[6] Zenker[7]), stomach

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* From the Snydacker Fund of the Michael Reese Hospital and the Nelson Morris Institute for Medical Research.

1. Rokitansky, C.: Lehrbuch der pathologischen Anatomie, ed. 3, Vienna, Wilhelm Braumüller **1**:303, 1855.

2. McCaskey, G. W.: The Clinical Association of Cancer and Tuberculosis with Report of a Case, Am. J. M. Sc. **124**:97 (July) 1902.

3. White, C. P.: A Note on the Association of Cancer with Tuberculosis, Lancet **1**:544 (March 14) 1925.

4. Friedländer, C.: Cancroid in einern Lungencarcinom, Fortschr. d. Med. **3**:307, 1885.

5. Schwalbe, E.: Entwicklung eines primären Carcinoms in einer tuberculösen Caverne, Virchows Arch. f. path. Anat. **149**:329, 1897.

6. Pepper, William; and Edsall, D. L.: Tuberculous Occlusion of the Esophagus with Partial Cancerious Infiltration, Am. J. M. Sc. **114**:44, 1897.

7. Zenker, K.: Carcinom und Tuberkel im selben Organ, Deutsches Arch. f. klin. Med. **47**:191, 1890.

and intestine (Naegeli [8]), regional lymph nodes (Clement [9]), breast (Warthin [10]), skin and other situations.

Lubarsch [11] points out five possibilities for the association of the two processes:

1. The purely accidental occurrence, with no influence of one on the other.

2. Near old tuberculous lesions and fresh miliary tuberculous eruptions, especially in tuberculous inflammation of the serous membranes, may be found metastasizing carcinoma in active growth. The carcinoma cachexia is a good nutritional basis for the dormant tubercle bacilli, and from the old nodules a new eruption results.

3. A fresh tuberculosis is added to a widely extending carcinoma.

4. Carcinoma is added to a chronic progressive tuberculosis, which serves as a "predisposing factor."

5. A hypothetical simultaneous occurrence of both processes.

Oertel [12] in a review of the subject concludes that the combination may exist in three forms:

1. The cancer may dominate, infiltrate the tuberculous granulation tissue and prevent a successful invasion by the tuberculous infection.

2. The tuberculous inflammation overgrows and destroys the cancer.

3. There exists a close association of the two diseases, "symbiosis," without any appreciable destructive influence of one on the other.

Some experimental work has been performed with the purpose of demonstrating the mutual exclusion or the possible interdependence of the two processes. Dixon, Smith and Fox [13] state that they have convinced themselves that tubercle bacilli or their products have a stimulating effect on epithelial structures.

Murphy,[14] and Murphy and Morton [15] have shown that the small mononuclear lymphocyte in the reaction zone about the tumor or in the

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8. Naegeli, O.: Die Combination von Tuberculose und Carcinom, Virchows Arch. f. path. Anat. **148**:435, 1897.

9. Clement, G.: Ueber seltnere Arten der Combination von Krebs und Tuberculose, Virchows Arch. f. path. Anat. **139**:35, 1895.

10. Warthin, A. S.: Coexistence of Carcinoma and Tuberculosis of the Mammary Gland, Am. J. M. Sc. **118**:25, 1899.

11. Lubarsch, O.: Ueber den primären Krebs des Ileum nebst Bemerkungen über das gleichzeitege Vorkommen von Krebs und Tuberculose, Virchows Arch. f. path. Anat. **111**:280, 1888.

12. Oertel, H.: Tuberculous Inflammation and Cancer, J. M. Res. **25**:504, 1911.

13. Dixon, S. G.; Smith, A. G., and Fox, H.: The Effect of Tubercle Products on Epithelium, J. A. M. A. **57**:800 (Sept. 2) 1911.

14. Murphy, J. B.: Heteroplastic Tissue Grafting Effected Through Roentgen-Ray Lymphoid Destruction, J. A. M. A. **62**:1459, 1914.

15. Murphy, J. B., and Morton, J. J.: Effect of Roentgen Rays on the Rate of Growth of Spontaneous Tumors in Mice, J. Exper. Med. **22**:800, 1915.

circulating blood constitutes the essential factor in the immunity mechanism to implanted tumors. Later Taylor and Murphy [16] asserted that "mice so x-rayed as greatly to reduce the lymphoid tissue are rendered highly susceptible to tuberculous infection. On the other hand, when a marked lymphocytosis is induced by first immunizing mice against and then inoculating them with cancer, the resistance to tuberculous infection is greatly enhanced. This heightened resistance may be set aside and even changed to a state of increased susceptibility to the infection by again depleting the lymphocytes by means of the x-ray."

A good deal of contrary evidence has been brought forward against these conclusions. Kessel and Sittenfield [17] reported that the administration of repeated doses of roentgen ray to guinea-pigs with experimentally induced tuberculosis was followed by healing of the tubercles by fibrosis, whereas no increased amount of lymphocytic reaction around the lesion was to be demonstrated. Sittenfield [18] later concluded that neither increase nor reduction of the lymphoid elements in the blood had any influence on either resistance or susceptibility to tumor growths.

Leaving the discussion of a possible etiologic relationship to a later paragrah, I shall tabulate the reported cases of carcinoma and tuberculosis of the uterus and report one additional case.

REPORT OF CASES

CASE 1.—*History.*—Mrs. A. L. E., a patient of Drs. Kahlke and Blackmarr, aged 47, had previously been curetted by a surgeon in another city for irregularity of menstruation and failing strength. The tissue removed was diagnosed microscopically as carcinomatous. In January, 1920, laparotomy was performed; this revealed free fluid in the peritoneal cavity and an inoperable carcinoma of the uterus. The abdomen was closed without further interference. In February, 1920, Dr. Kahlke performed a diagnostic curettage and found an adenocarcinoma of the uterus. Ninety milligrams of radium were inserted for twenty-four hours. In May menstruation had ceased, and her weight was normal. In February, 1923, there was a slightly bloody discharge from the uterus, which had appeared first in January, 1923, having been absent since the first radium treatment in 1920. She was examined again in September, 1924, at which time she was feeling unusually well except for the slight discharge, at times watery, occasionally a little bloody. Pelvic examination revealed no gross pathology in the way of masses or fixation. No glands could be felt by rectum or vagina, and there was no evidence of metastases to bone or of involvement of the supraclavicular glands. Fifty milligrams of radium were inserted for six hours in January, 1924. At this time her chest and lungs revealed no positive findings. A senile vaginitis was present which ceased after the radium insertion. In April, 1925, she returned

16. Taylor, H. D., and Murphy, J. B.: Effect of Cancer Immunity on Resistance to Tuberculosis, J. Exper. Med. **25**:609, 1917.

17. Kessel, L., and Sittenfield, M. J.: The Effect of Penetrating Rays upon Experimental Tuberculosis, Proc. New York Path. Soc. **14**:190, 1914.

18. Sittenfield, M. J.: The Significance of the Lymphocyte in Immunity to Cancer, J. Cancer Res. **2**:151, 1917.

to the Chicago Memorial Hospital, at which time she complained of extreme weakness and a slight loss of weight—8 pounds (3.6 Kg.). On examination the breath sounds were clear, and the lungs were resonant throughout. There was slight tenderness on deep pressure around the umbilicus. Nothing suggested metastasis. The temperature and blood count were normal. A low laparotomy was performed. The uterus was the size of a pear, rough and soft. Free amber-colored fluid was found in the peritoneal cavity. No palpable or visible metastases to the peritoneum, liver or other organs were seen. No palpable glands were noted in the pelvis, but some were felt along the large vessels in the upper part of the abdomen. Panhysterectomy was performed.

Macroscopic Examination.—The uterus, which was removed supravaginally, measured 6 by 8 by 1.4 cm. Arising from a broad base in the body of the uterus, 2 to 3 cm. narrower than the width of the specimen, was a large, papillary, friable mass projecting into the uterine cavity and completely filling the latter. At the base of this tumor the tissue was not well defined or sharply delimited. The tumor tissue was frequently necrotic, but there were no definite caseating areas. In the myometrium the vessels stood out prominently, and the muscle appeared to be interspersed with fibrous tissue, but no definite tumor tissue or any nodular aggregations could be seen macroscopically. The external surface of the uterus was ragged and thickened; there were no nodular projections on it. The right tube and ovary were attached, and in the broad ligament, subjacent to the proximal end of the ovary and embedded in the external coat of the uterus there was a soft, whitish, irregular nodule appearing like tumor tissue. The ovary on this side was scarred and firm, and measured 3 by 1.5 by 0.7 cm. It presented no obvious gross abnormalities. The corresponding tube measured 5 by 0.5 cm. It appeared thin and fibrotic, but otherwise normal. The fimbriae were open. The other tube and ovary were unattached to the specimen, and showed no gross abnormalities.

Microscopic Examination.—The tissue was fixed in formalin and embedded in paraffin. The structure of the tumor mass (fig. 1) was that of a dense collection of glandlike spaces frequently having a pinkish, homogeneous substance within their lumina. These spaces were lined by a high cuboidal epithelium with an oval nucleus in the longitudinal axis of the cell. The cells were arranged on an edematous, thin framework which was papillary in the sections taken longitudinally. Mitoses in the epithelial cells were numerous. Superficially there was considerable necrosis of the tumor, and the stroma appeared to be converted into a homogeneous, slightly fibrillar mass in which a few nuclei could be seen. These branching masses were often surrounded by a layer of fairly intact epithelial cells. In the stroma, also, numerous, large mononuclear wandering cells with coarse, brownish-yellow pigment granules in their cytoplasm were found at several points. In one small area the epithelium about a bit of homogeneous stroma was apparently changing into squamous epithelium, even to the formation of a stratum granulosum. In none of the sections through the tumor or involved endometrium were there any tubercles. Where the necrosis of the tumor was marked there was frequently an adherent exudate of fibrin on the surface, and enmeshed in this fibrin were numerous neutrophilic leukocytes. The endometrium beyond the tumor was very thin with a small amount of stroma. The epithelium, however, was fairly high, but not proliferating. The endometrial glands in these areas were scanty and frequently dilated.

In one section the endometrial surface dipped inward into the myometrium for a considerable depth. A few glandular spaces surrounded by typical endometrial stroma were found beneath the general level of the myometrium, thus

producing the appearance of an endometriosis. In this same section, superficially, the endometrium became markedly thickened and papillary and similar in appearance to that of the tumor. This papillary growth tended to extend along the clefts into the myometrial tissue. In the streaks of myometrial tissue thus established there were several cellular areas consisting of large cells with irregularly oval vesicular nuclei and deeply staining, slightly vacuolated cytoplasm. These cells were surrounded by a dense zone of lymphocytes. At the margin of an area there was a giant cell with peripheral oval nuclei and finely vacuolated central cytoplasm. The outer surface of this section was covered by serosal mesothelium. Adherent to the latter was a layer of hemorrhagic fibrous tissue. There was no tubercle formation in this layer, but at one edge there was a clump

Fig. 1.—General structure of the tumor. The section is taken from the papillary mass projecting into the endometrial cavity; × 60.

of tumor cells similar to those of the tumor itself. This section was taken from the uterus below the right cornu and adjacent to the bit of whitish tumor-like substance in the broad ligament, described under "Macroscopic Examination." Other sections through the myometrium showed scattered typical tubercles consisting of a central giant cell with peripheral nuclei and deeply staining finely vacuolated cytoplasm, surrounded by epithelioid cells and an outer dense zone of lymphocytes. Some areas contained no giant cells. They were frequently in direct proximity to lymphatics which were widely open (fig. 2). Other lymphatics in the myometrium frequently had a mantle of lymphocytes about them. The intima of the myometrial vessels was greatly thickened, some of the vessels being

occluded; the walls were hyaline. The superficial muscle tissue was dense, but deeper down the muscle bundles were separated by edema. These edematous areas were often sparsely infiltrated with lymphocytes.

In one section the epithelial tumor masses were seen within lymphatics in the myometrium a slight distance beneath the tumor. Tubercles were present in the subserous outer layer of this section.

A section through the broad ligament between the ovary and uterus, that is, through the whitish tumor-like area described in the gross, showed that it consisted of several large islands of epithelial cells having marked tendency toward gland formation, marked variation in chromatin content of the nuclei, and fairly frequent mitoses (fig. 3). About these areas, although not immediately in contact with them, were several giant cell tubercles. Two areas at the periphery of the section consisted of compact conglomerate giant cell and epithelioid tubercles surrounded by a zone of fibroblasts. There was no caseation.

Another bit of tissue from the broad ligament showed similar clumps of epithelium forming gland-like spaces, often becoming papillary and resting on a thin stroma. About the larger clumps there was some fibrous tissue encapsulation, and this tissue contained numerous large mononuclear wandering cells, lymphocytes and plasma cells. In this section, however, there was no tubercle formation. Occasionally the epithelial cells appeared degenerated, and when this occurred there was an infiltration of leukocytes, sometimes almost filling the glandular spaces.

All the sections through the tube failed to reveal any tuberculous involvement. The epithelium of the villi was fairly low but normal in appearance. The villi were markedly thickened and fibrous. There was also an increase in fibrous tissue in the wall. Sections were taken from both proximal and distal portions of the tube.

In a section through the ovaries, there was marked hyalinization of the walls of the vessels and obliterating endarteritis. Corpora albicantia and fibrosa were numerous. Several small areas near the surface consisting of large vacuolated cells with a small central nucleus were quite vascular and appeared like abortive follicles.

Attempts were made to demonstrate the tubercle bacillus in the granulomatous lesions. Several methods were employed; the Ziehl-Neelsen, Koch-Ehrlich, MacCallum bacterial stain and various modifications as they suggested themselves. With none of the methods could the bacilli be demonstrated satisfactorily. A gram-positive rod was found in the cytoplasm of a giant cell stained by the MacCallum method. That this failure to demonstrate the bacilli was not exceptional is attested by the fact that several of the authors to be quoted noted the remarkable difficulty in finding the organism in the uterus and its appendanges. It is notoriously difficult to stain the tubercle bacillus in tissues fixed in formalin (Schmorl).[19]

The study of this specimen leads to the conclusion that the tumor obviously was malignant; that it was a papillary adenocarcinoma of the body of the uterus involving almost the entire endometrial surface, extending through the wall of the uterus to the peritoneal surface and into the broad ligament. This extension was probably largely lymphatic. Whether the tumor originated from the surface epithelium or the glands is difficult to decide. The appearance at the edge of the growth would lead one to believe that it had originated from the proliferating surface epithelium.

19. Schmorl, G.: Die pathologisch-histologischen Untersuchungsmethoden, ed. 10 and 11, Leipzig, F. C. W. Vogel, 1921, p. 31.

The carcinoma was old, at least five years as judged from the time of the patient's first curettement, when it was discovered.

The involvement of the myometrium by the granulomatous areas is believed to be tuberculous. No evidence of foreign bodies or of syphilitic infection could be obtained. The tubercles are histologically noncaseous and evidently quite young. Their diffuse distribution and the equality of development in all the sections would augur for a simultaneous sprinkling over a fairly large area. None of them was found in the tumor tissue itself. They are never in direct continuity with the tumor tissue itself and apparently have no bearing on its origin. However, serial sections in a large number of places might reveal a more intimate relationship. Even if this were so, the etiologic connection, that is, that the tumor was secondary to the irritating and proliferative influence of the tuberculosis, is ruled out by the temporal relationship of the two processes. There was no evidence of adnexal or peritoneal tuberculosis. Unfortunately, the cervix was not removed and could not be investigated. We assume, therefore, that the tuberculous involvement was secondary, and that it probably was hematogenous or lymphogenous from a distant focus or foci. The association would then be purely accidental, and the only possible etiologic bearing of the one process on the other would be that the tumor acted as a favorable nidus for the development of the tuberculous affection.

The patient left the hospital in good condition, and six months later reported herself in excellent health.

There is a fairly extensive literature on the isolated instances of the occurrence of the two processes in the uterus, but very little has appeared in the American medical literature. The comprehensive reviews of von Franqué [20] and Wallart [21] are the most exhaustive of the older literature and summarize well the cases reported up to the time of appearance of their articles.

Case 2.—The first case was reported by von Franqué [22] in 1894. This is identical with the case discussed by Nassauer [23] in his inaugural dissertation. It concerns itself with a woman, aged 43, operated on for carcinoma of the portio vaginalis. The carcinomatous infiltration reached almost to the internal os but did not extend beyond it. The mucosa of the cervix was intact. Two centimeters above the internal os was a small nodule surrounded by normal endometrium. Near it was a smaller similar nodule. There were small myomas in the wall of the fundus. Microscopically it was demonstrated that the nodules in the corpus were beginning tuberculous areas associated with adenomatous hyperplasia of the glands and atypical epithelial hyperplasia, described in this connection for the first time. It was pointed out that the epithelium of the uterine glands as well

20. Von Franqué, O.: Ueber das gleichzeitige Vorkommen von Karzinom und Tuberkulose an den weiblichen Genitalien, insbesondere Tube und Uterus, Ztschr. f. Geburtsh. u. Gynäk. **69**:409, 1911.

21. Wallart, J.: Ueber die Combination von Carcinom und Tuberculose des Uterus, Ztschr. f. Geburtsh. u. Gynäk. **50**:243, 1903.

22. Von Franqué, O.: Zur Histogenese der Uterustuberculose, Sitzungsberichet der phys. med. Gesellsch. Würzburg, March 3, 1894.

23. Nassauer, M.: Ein Fall beginnender Tuberculose der Gebärmutterschleimhaut bei fortgeschrittenem Cancroid der Portio Vaginalis, Innaug. Diss., Würzburg, 1894, cited by von Franqué.

as the stroma cells could change into epithelioid and giant cells. Von Franqué believed that the tuberculous process was the older and had extended from the tubes.

Case 3.—Frees[24] reported a case of typical peritoneal tuberculosis with ascites (case 11). The tubes were not described, but an incipient carcinoma of the portio was found by biopsy. Later the patient was observed with a papillary "cancroid" of the portio, and died during the same year.

Case 4.—Von Recklinghausen[25] in his book on adenomyoma and cystadenoma describes a case (case 14) in which in one portion of an "adenomyoma" there were carcinomatous changes in the epithelium of the glandular elements plus tuberculosis.

Fig. 2.—A tubercle deep in the myometrium, well removed from any epithelial structure, the lymphocytic mantle projecting into a widely dilated lymphatic; × 130.

Case 5.—Bass,[26] working in Ribbert's Institute, described a case in a woman, aged 61, in whom necrospy revealed a large, partially necrotic, cervical carcinoma that had involved the wall of the corpus and the vagina. In the fundus

24. Frees, G.: Die operative Behandlung des tuberkulösen Ascites, Deutsch. med. Wchnschr. **20**:849 (Nov. 8) 1894.

25. Von Recklinghausen, O.: Die Adenomyome und Cystadenome der Uterus und Tubenwandung, Berlin, A. Hirschwald, 1896, p. 16.

26. Bass, O.: Ein Fall von Carcinom und Tuberculose des Uterus, Inaug. Diss., Zürich, 1899, cied by Wallart.

the endometrium was markedly distorted, and on it there were different sized and shaped excrescences projecting into the cavity. These were tuberculous, caseous, with a marked tendency toward deep extension. There were tubercles beneath the serosa with infrequent giant cells, marked caseation and many tubercle bacilli. Both tubes were thickened and caseous. In the lungs there were numerous old tuberculous nodules. Bass concluded that because of the pronounced separation of the two processes an etiologic relationship must be decried.

CASE 6.—Ahlfelder[27] described a case (case 3) which at operation showed peritoneal tuberculosis and caseous tubercles in immediate proximity to a typical adenocarcinoma uteri. Tubercle bacilli could be demonstrated.

CASE 7.—Kundrat[28] reported the case of a woman, aged 36, who died following an operation for carcinoma of the portio vaginalis. At necropsy there were minute tuberculous nodules in the left apex of the lung, but no intestinal tuberculosis. In the uterus there was a large carcinoma of the portio vaginalis, most marked in the anterior lip, and which reached almost to the internal os. It was a cylindrical cell carcinoma, and it could not be determined whether it arose from the cervical glands, cervical epithelium or erosion glands. The mucosa of the endometrium showed an endometritis glandularis. The tubes were tuberculous, and their mucosa showed (von Franqué) markedly atypical carcinoma-like proliferation. In a lymph node of the lesser pelvis there was an epithelioid tubercle surrounded by carcinomatous tissue. Kundrat believed his case to be the first reported, but it was several years later than the report of von Franqué.

CASE 8.—Heinsius[29] cited a case of a nullipara, aged 40, whose uterus was enlarged and anteflexed. The right adnexa were buried in adhesions. In the left cornu there was a small apple-sized myoma. The endometrium was markedly thickened. Microscopically in the same field there were partially caseous tubercles next to unmistakable adenocarcinoma.

CASE 9.—Stein[30] discussed a case in a virgin, aged 48, whose mother died nine years previously from carcinoma of the uterus. The thoracic organs were normal. Eight days after a total hysterectomy, death occurred. The right tube showed old caseous tuberculosis. The fundus of the uterus was occupied by a large, degenerated, caseous and crumbly cavity in the walls of which grayish-yellow nodules could be seen. Microscopically there were found in the walls of the tubes, and especially in the uterus, many caseous epithelioid and giant cell tubercles closely surrounded by pegs and strands of large, flat, chromatin-rich cells. In the larger collection of these cells a glandular formation was noted. The carcinoma was a squamous cell epithelioma derived from the portio, extending through the right half of the uterus and metastasizing through the lymphatics into the tubes. No bacilli could be demonstrated in the tubercles. Stein believed the tuberculosis to be the older process.

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27. Ahlfelder, C.: Klinische und anatomische Beiträge zur Genitaltuberculose des Weibes, Monatschr. f. Geburtsh. u. Gynäk. **16**:296, 1902.

28. Kundrat, R.: Zur Tuberkulose der Tuben und der Uterus mucosa, Arch. f. Gynäk. **65**:75, 1902.

29. Heinsius, O.: Die Therapie des Carcinoma Uteri an der Grieswalder Fraunenklinik, Esgängungsb. klin. Jahrb., ed. 2, Jena, J. Springer, 1902.

30. Stein, A.: Beiträge zur Kenntnis der Entstehung des Gebärmutterkrebses, Monatschr. f. Geburtsh. u. Gynäk. **17**:209, 1903.

CASE 10.—Wallart [31] described three cases from the material at Basel under the directorship of E. Kaufmann.[31] In the first case, the curetted material from a woman, aged 55, showed partially confluent caseous tubercles with giant cells closely surrounded by adenocarcinomatous masses with sparse alveolar formation. No further details were known.

CASE 11.—The second case in his series was a necropsy specimen from a woman, aged 50, with chronic lung, intestinal and peritoneal tuberculosis. There was bilateral tuberculous salpingitis and caseation of the uterine wall and cervix. In the cervix a widely progressive carcinoma was also developing from the glandular epithelium. The association of the two processes was remarkably intimate, so that in areas it was difficult to determine which was carcinomatous and which tuberculous. In the cervical glands atypical epithelial proliferation was present, and tubercle bacilli were demonstrable. The direct transition of this atypical proliferation of the cervical epithelium to carcinoma could be shown.

CASE 12.—Wallart's third case concerned a woman, aged 37, who died of tuberculous meningitis and who had an adenocarcinoma of the portio vaginalis at necropsy. In addition there was a tuberculous nodule in the right side of the endometrium of the body, 1 cm. below the tubal opening. This nodule was caseous, without definite tubercle or giant cell formation. Tubercle bacilli could be demonstrated. The contiguous epithelium and glands showed a proliferative reaction. The carcinoma and tuberculosis were widely separated.

CASE 13.—Von Franqué's [32] second case was that of a sextipara, who was operated on for a disseminated "portio cancroid." There was marked ascites. The peritoneum of the corpus, the cervix, the vagina and the intestine was covered by tubercles identified microscopically. No note was made of the condition of the endometrium and the tube.

CASE 14.—Schottländer [33] in his discussion concerning the early histologic diagnosis of tuberculosis stated that he had seen a case in which atypical epithelial proliferation was the result of tuberculous involvement, and in which carcinoma of the cervix developed as a result of the tuberculous irritation.

CASE 15.—De Josselin de Jong [34] related a case in a woman, aged 64, the curettement from whom showed tuberculosis and carcinoma. In the operation specimen it was believed that tuberculosis of the endometrium first developed, then a carcinoma of the cervix, which was later infected by the tuberculosis of the corpus.

CASE 16.—Schütze [35] wrote of a specimen of adenocarcinoma of the cervix with a diffuse adenoma of the corpus uteri which was tuberculous. He was unable

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31. Kaufmann, E.: Spezielle pathologische Anatomie, ed. 7 and 8, Berlin, Walter deGruyter **2**:1282, 1922.

32. Von Franqué, O.: Beiträge zur Lehre von der Bauchfell und der Genital tuberculose beim Weibe, in Hofmeier: Die Universitäts-Frauenklinick zu Würzburg, Stuttgart, Enkes, 1903.

33. Schottländer, J.: Zur histologischen Diagnose bei Frühstadien von Uterustuberkulose, Monatschr. f. Geburtsh. u. Gynäk. **21**:53, 1905.

34. De Josselin de Jong, R.: Een Geval van carcinoma et tuberculosis uteri, Nederl. Tijdschr. v. Verlosk. en Gynaec. **16**:89, 1905; abstr., Monatschr. f. Geburtsh. u. Gynäk. **23**:114, 1906.

35. Schütze, A.: Eine seltene Beobachtung der Kombination von Karzinom, diffusem Adenom und Tuberkulose, nebst Bildung von Psammomkörpern im Uterus einer 40 jährigen Nullipara, Ztschr. f. Geburtsh. u. Gynäk. **60**:540, 1907.

to demonstrate tubercle bacilli in his specimen. The tubes were not removed, but their openings into the uterus were tuberculous. The carcinoma was entirely free from tuberculous involvement. The epithelium of the endometrial glands showed isolated instances of proliferation. He believed the cervical carcinoma to be the primary affection.

Case 17.—Eisenstein [36] presented as the last of his series of five cases of carcinoma of the uterus (cervix) a woman, aged 24, with portio carcinoma and with tuberculous salpingitis and endometritis.

Case 18.—D'Halluin and Delval [37] reported the case of a woman, aged 35, presenting a familial tendency toward tuberculosis. She was operated on for a uterine tumor. The specimen was an irregular mamelonated mass riddled with

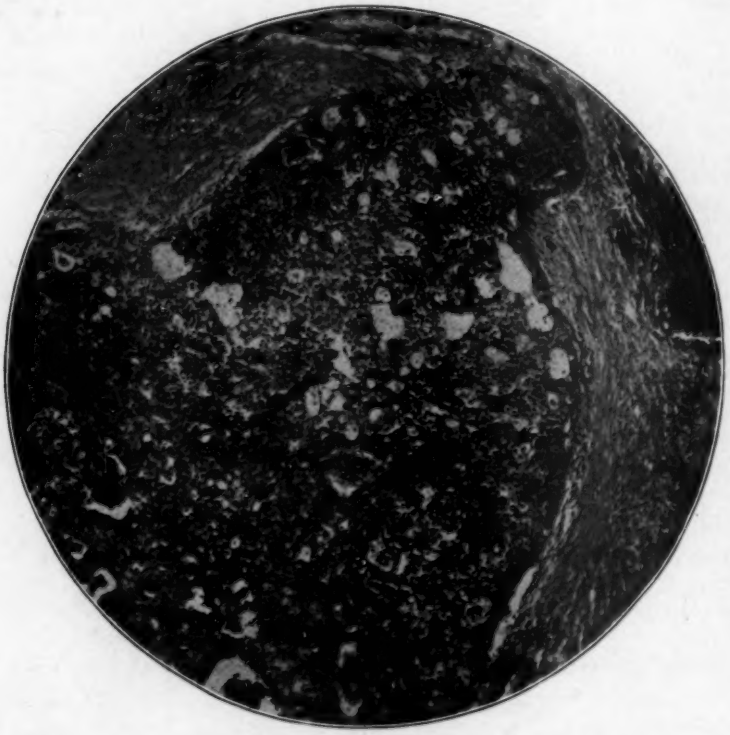

Fig. 3.—A mass of metastatic tumor tissue in the broad ligament proximal to the ovary and beneath the uterine end of the tube; × 60.

spaces so as to appear spongelike. It was impossible to determine which was cavity or to determine the demarcation between uterus and adnexa. The microscopic picture was that of a cylindrical cell carcinoma of the corpus uteri. Many typical epithelioid and giant cell tubercles were found between the carcinomatous columns. No tubercle bacilli could be demonstrated.

36. Eisenstein, K.: Genitaltuberkulose mit Portio Krebs, Gyógyászat **48**:449, 1908; abstr., Zentralbl. f. Gynäk. **30**:128, 1910.

37. D'Halluin, M., and Delval, C.: Cancer de l'uterus et tuberculose associaée, Bull. et mém. Soc. anat. de Paris **85**:772, 1910.

CASE 19.—In his review of 1911 von Franqué [38] reported two additional cases. The first patient was a sterile woman, aged 38, who on operation for an adnexal tumor revealed slight ascites, a large left and a smaller right adnexal tumor, with fine, papillary metastases in the uterus and bowel. Gross examination showed a few interstitial myomas and the right tube transformed into an egg-shaped tumor. A larger, similar tumor was present in the left side. Microscopically the muscularis of the uterus was free from tuberculosis. In the endometrium there were isolated typical giant cell and epithelioid tubercles; the epithelium of the glands near the latter was hyperplastic. The ovary was normal. In the tubes there was a thickened subserosa with carcinoma implantation. The muscularis showed round cell infiltration but no typical tubercles. In the mucosa there were widely extending tuberculous changes. The left tube showed similar changes with transformation into carcinoma. Von Franqué believed that he was dealing with a chronically progressive tuberculosis older than the carcinoma.

CASE 20.—Von Franqué's last case was that of a woman, aged 40, operated on seventeen years previously for tuberculous ascites. There was a very old bilateral tuberculosis and miliary tuberculosis of the corpus uteri and cervical mucosa. In the latter, partially in close proximity to and partially removed from the tuberculous changes there was carcinomatous transformation of the glandular and superficial epithelium. The tuberculous atypical epithelial proliferations were found only in the cervical mucosa but separated from the carcinoma. The carcinoma proceeded directly from the cervical epithelium, not from the tuberculous atypical epithelium.

CASE 21.—Mönckeberg [38] shared in the discussion at the demonstration of von Franqué's preparation, and related that he had found an adenocarcinoma of the corpus uteri separated from a squamous cell carcinoma of the cervix, combined with solitary tubercles in the endometrium. He considered the latter accidental.

CASE 22.—Vanverts [39] reported a case of epithelioma of the uterus and caseous tuberculosis of the tube. Beyond the tuberculous involvement the epithelium of the tube showed considerable papillary proliferation.

CASE 23.—Lipschitz [40] discussed a case in a nullipara, aged 44, the uterus from whom showed a few intramural myomas. The thickened, tortuous right tube had typical giant cell and epithelioid tubercles in its midportion. In the fimbria there was a papillary carcinomatous growth plus a few tubercles. The tuberculosis was believed to be primary. He cited a case of Friedenheim's with similar characteristics. The reference to this case could not be obtained.

CASE 24.—Schmidt [41] described the uterus removed from a woman, aged 55, who died suddenly after a total hysterectomy for a squamous cell carcinoma plus tuberculosis of the cervix revealed at biopsy. At necropsy there were no metastases, but many conglomerate tubercles in the right kidney and old bilateral apical scars. The uterus was small. The adnexa were normal. The cervix was infiltrated with squamous cell carcinoma with marked pearl formation and frequently central

38. Mönckeberg, J. G., cited by von Franqué (footnote 20).

39. Vanverts, J.: Coexistence d'une tuberculose de la trompe et d'un épithélioma de l'utérus, Rev. mens. de gynéc., d'obst. et de pédiat. **7**:571, 1912.

40. Lipschitz, K.: Ein Fall von primärem Tubenkarzinom auf dem Boden alter Tuberkulose, Monatschr. f. Geburtsh. u. Gynäk. **39**:33, 1914.

41. Schmidt, E.: "Tuberkelknötchen" in einem Portiokarzinom, Beitr. z. Geburtsh. u. Gynäk. **19**:315, 1914.

necrosis of the carcinoma cell clumps. Bounding the carcinomatous masses near the hornified layers of epithelium there were giant cell formations similar in appearance to tubercles. No bacilli could be demonstrated. Schmidt felt inclined to believe that the tuberculosis, if one might call it such, was secondary. He also tended toward the belief that the tubercle-like reaction was really the result of the formation of foreign body giant cell granulomas, the foreign body being the hornified substance of the degenerated carcinomatous pegs.

Case 25.—Stacy and Nelson [42] reported briefly a case clinically diagnosed as a left cystic ovary and hydrosalpinx, which on operation revealed itself to be a papillary carcinoma of the tube and ovary. Both tubes were tuberculous, apparently quiescent. Multiple myomas were present in the ovary, the endometrium was "polypoid" and the vessels sclerosed. No histologic description was presented, and no bacillary staining was reported.

Case 26.—Strachan's [43] patient was a woman, aged 40, in whom pulmonary tuberculosis was suspected, but with no bacilli in the sputum. The cervix was occupied by a hard, gray, squamous cell carcinoma with hornification and cell nest formation. The isthmus was free of change. The corpus uteri was distended and filled with caseating material. Microscopically the endometrium was a loose, fibrocellular meshwork thickly infiltrated with lymphocytes and at intervals showing giant cells, singly or in clusters. In some instances the giant cells were surrounded by a layer of epithelioid cells with an outer zone of lymphocytes.

White,[3] in the summary of cases of association of cancer and tuberculosis, cited case 5 of the foregoing series as a combined lesion of columnar carcinoma and tuberculosis of the uterus, but there was also carcinoma in the stomach and ovaries, so that the uterine process could not be considered definitely as the primary focus of carcinoma. The tuberculosis, he believed, was obviously secondary.

CLINICAL NOTES AND DISCUSSION

I have collected, therefore, twenty-eight cases in which the combination of the two processes was found. There are included, in addition to the cases abstracted above, that of Friedenheim cited by Lipschitz, White's case and my own. Four of the cases are tubal carcinomas, eight are adenocarcinomas of the body of the uterus and sixteen are squamous and cylindrical cell carcinomas of the cervix. In the eighteen cases in which the age of the patient was noted, one was in the second decade, four in the third, seven in the fourth, three in the fifth and three in the sixth. Of course, with so few cases one cannot conclude with certainty, but it is interesting that the greater age incidence (late adult life) was in the period of greater frequency of carci-

42. Stacy, Lida J., and Nelson, O. C.: Report of Three Cases: Adenocarcinoma of Ovary and Tube with Tuberculosis, Fibromyoma in Hernial Sac and Solid Carcinoma of the Left Ovary, M. Clin. N. Amer. **7**:173 (July) 1923.

43. Strachan, G. I.: Combined Carcinoma and Tuberculosis of the Uterus, J. Obst. & Gynec. Brit. Emp. **31**:289, 1924.

noma and in the period of the lesser frequency of active tuberculosis. The lesions occurred in virgins, nullipara and multipara.

Clinically the diagnosis before operation was usually that of the tumor process. The tuberculous involvement was unsuspected in most instances, unless found in the biopsy or curetted material. There does not appear to be any sign or symptom or combination of signs which would lead one to diagnose the conditions present. The symptoms are usually of a malignant genital tumor or of pelvic inflammatory disease. Often these are combined. The tumor is most often the element which produces the symptoms for which the patient seeks relief. The tuberculosis produces little symptomatology, although in the case of Schütze metrorrhagia was present years before the development of the tumor. A tumor in a person with a known tuberculous focus should lead one to suspect the simultaneous occurrence of the two processes. Biopsy or curettement are the only means of positive diagnosis.

In the introductory paragraphs it was pointed out that there is a diversity of opinion regarding the causal relationship of the two processes. The results of experimental work are not conclusive. Von Franqué described atypical epithelial proliferation in his cases and suggested that the tumor was secondary to the tuberculosis. Wallart, in discussing his case, also expressed the belief that the tuberculosis had caused a proliferative reaction of the cervical glandular epithelium which had overstepped the normal boundaries and developed into carcinoma. Stein was in accord with him in the discussion of his case. In nine of the sixteen cases cited by von Franqué, the latter believed that the tuberculosis was primary. He proposed that the carcinoma developed as a result of the chronic prolonged irritant effect of the tuberculous juices on the epithelium. Undoubtedly this is possible. It has been shown to occur in the skin, and possibly in the intestines. The case here presented shows no such relationship. The temporal relationship itself is sufficient proof of primary involvement by the tumor.

The neoplasm was of at least five years' duration. That it had not earlier caused more widespread involvement of the uterus was probably due to the fact that it began as a papillary tumor which invaded the underlying uterine tissues only at a later stage of its development. The tubercles present in the myometrium are histologically of much shorter duration than the time which can be ascribed to the tumor. They are young, are free of caseation, and have apparently resulted from a recent ensemination of the myometrium from an older focus elsewhere in the body. The serosa of the uterus and its adnexa was not involved by the tuberculous process, nor was there any evidence of generalized peritoneal tuberculosis at the time of removal of the uterus. The myometrial tuberculosis, cannot, therefore, be looked on as an

involvement by continuity from the peritoneum or from an older focus in the internal genital tract. The presence of the tumor may have been a factor in rendering the uterus susceptible to infection by tubercle bacilli derived from an older process situated outside the genital tract.

SUMMARY

In a case of associated tuberculosis and carcinoma of the body of the uterus, the later process was apparently the older one, the tuberculosis developing later as the result of the localization of bacilli from an older distant focus.

From the literature twenty-seven cases in which tuberculosis was associated with carcinoma of the uterus and its adnexa have been summarized.

Of the total twenty-eight cases now on record, four were tubal carcinomas, eight were carcinomas of the body of the uterus, and sixteen were carcinomas of the cervix.

In a small proportion of the reported cases the chronic inflammation of the tuberculous process was believed to have been a factor in the development of the carcinoma. In the remaining cases the association appears to have been purely accidental, with a possibility that the presence of the neoplasm may have rendered the uterus more susceptible to tuberculous infection.

The preoperative diagnosis of the presence of both conditions has been made three times from curetted or excised material. In general, the clinical diagnosis has been tumor, the tuberculosis being discovered during the later examination of the removed tissue.

FOLLICULOMA OVARII

REPORT OF A CASE *

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Among the solid tumors of the ovary, the least frequently encountered is that type of carcinoma to which Gottschalk [1] has given the name folliculoma malignum ovarii. The frequency of its occurrence may be judged by the experience of Aschner,[2] who in 1921 was able to find only twenty-four cases reported in the literature, to which however there have been several subsequent additions. The specimen which I examined differs from those previously described by other observers in the uniformity of its structure.

CASE REPORT

The tumor was removed from a widow, aged 52, who had borne three children. Menstruation had ceased from April to October, 1923, and since that time she had menstruated irregularly at intervals of approximately two weeks. Recently, menstruation had been accompanied by nausea.

Physical examination was essentially negative, except for the loss of 2 pounds (0.9 Kg.) in weight and the presence of a hard smooth mass in the culdesac of Douglas, the mass extending almost to the umbilicus. A right salpingo-oophorectomy and a left salpingectomy was performed on March 16, 1925.

In the gross, the tumor was solid, firm and roughly oval, measuring 18 cm. in its longest, and 12 cm. in its greatest, transverse diameter. The surface was grayish-white, smooth and glistening, with an occasional area of hemorrhage on the surface. On section the surface had the same grayish-white appearance, and felt spongy and semi-elastic. Here and there were small cysts (0.5 cm. in diameter) containing a dark, bloody-looking fluid. Both fallopian tubes were without gross abnormality.

Histologic examination of the fallopian tubes disclosed as the sole lesion a slight round cell infiltration of the submucous connective tissue with some increase of the connective tissue in this layer.

Microscopically, the general architecture of the neoplasm was that of a large number of roset-like alveloi held together by a stroma which closely simulated ovarian stroma. Detailed examination showed the stroma to be composed of spindle cells with relatively long fibrils, and lightly staining, somewhat vacuolated cell bodies. In some areas these fibrils were closely packed together, in others separated by interstitial edema and small areas of interstitial hemorrhage. While the stroma supported the alveoli, there were in evidence many open spaces apparently originally filled by alveoli which had dropped out of the tissue during the course of preparation.

The epithelial elements of the growth consisted of columnar epithelial cells of considerable size. These were arranged as rosets with the nuclei at the periphery.

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* From the Achelis Laboratory of the Lenox Hill Hospital.

1. Gottschalk: Arch. f. Gynäk. **59**:676, 1899.
2. Aschner: Arch. f. Gynäk. **115**:350, 1921.

The cell cytoplasm was either granular or slightly foamy and took a deep eosin stain; while with sudan III, numerous fat droplets which were doubly refracting when examined with a Nichol's prism were demonstrable at the nuclear end of the cell. The nuclei were somewhat vacuolated, and deeply staining and mitotic figures were rarely observed. No matter in which plane the sections were cut, the alveoli did not present as solid strands (fig. 1). Apparently if reconstructed, they would appear as globoid bodies and not as finger-like processes.

The individual acinus or roset occurred in a variety of forms. In some the margins of the cells (the portion of the cell away from the nucleus) met and

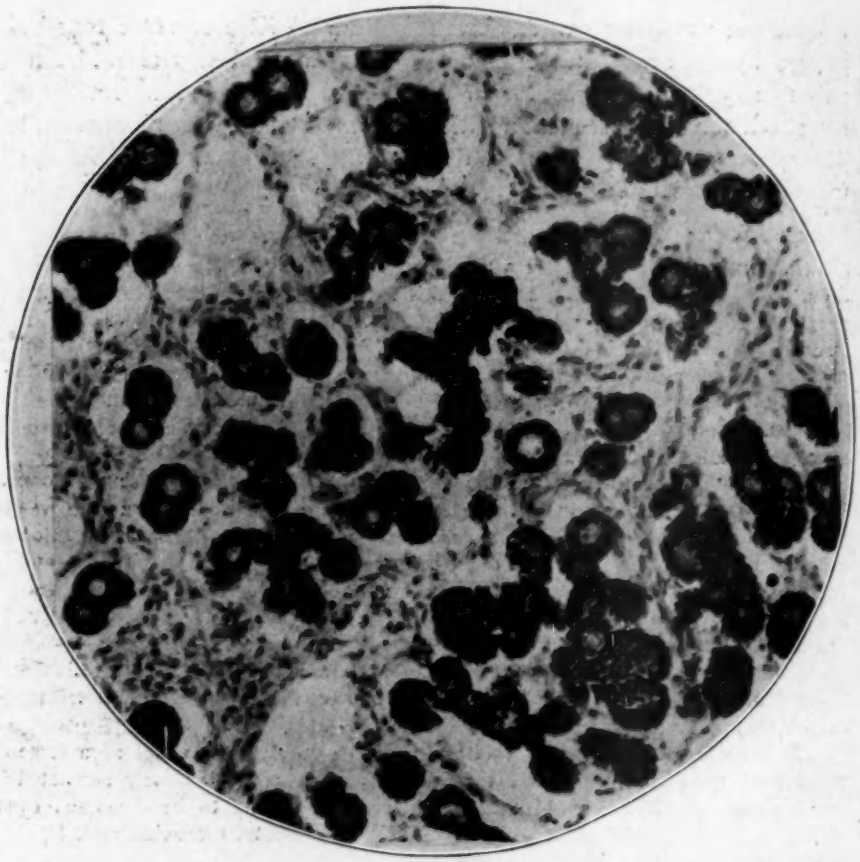

Fig. 1.—Showing globoid character of rosets, with numerous so-called follicle cells; × 250.

there was no lumen in the unit, while in others there was a distinct lumen of varying diameter. In the center of units possessing a lumen, brown doubly refracting fat globules were at times encountered, while in other instances the lumen was clear. In approximately 30 per cent of the units, an isolated cell was found in the unit lumen which differed in its characteristics from the cells of the roset. This cell was polyhedral, with a clear cytoplasm, and had in its center a deeply staining mass of chromatin, apparently a nucleus (fig. 2). Fat was not

demonstrable in the cell. While at times the cell would be attached to or in contact with the cells of the roset, more often it lay free in the lumen. Mitotic figures were not observed in these cells.

This woman was a patient of Dr. Donald Miner, Jersey City, N. J., to whom we are indebted for the clinical data.

COMMENT

The first descriptions of tumors of this type were made by Acconci [3] and Lonnberg.[4] Emanuel,[5] describing a similar case, considered the

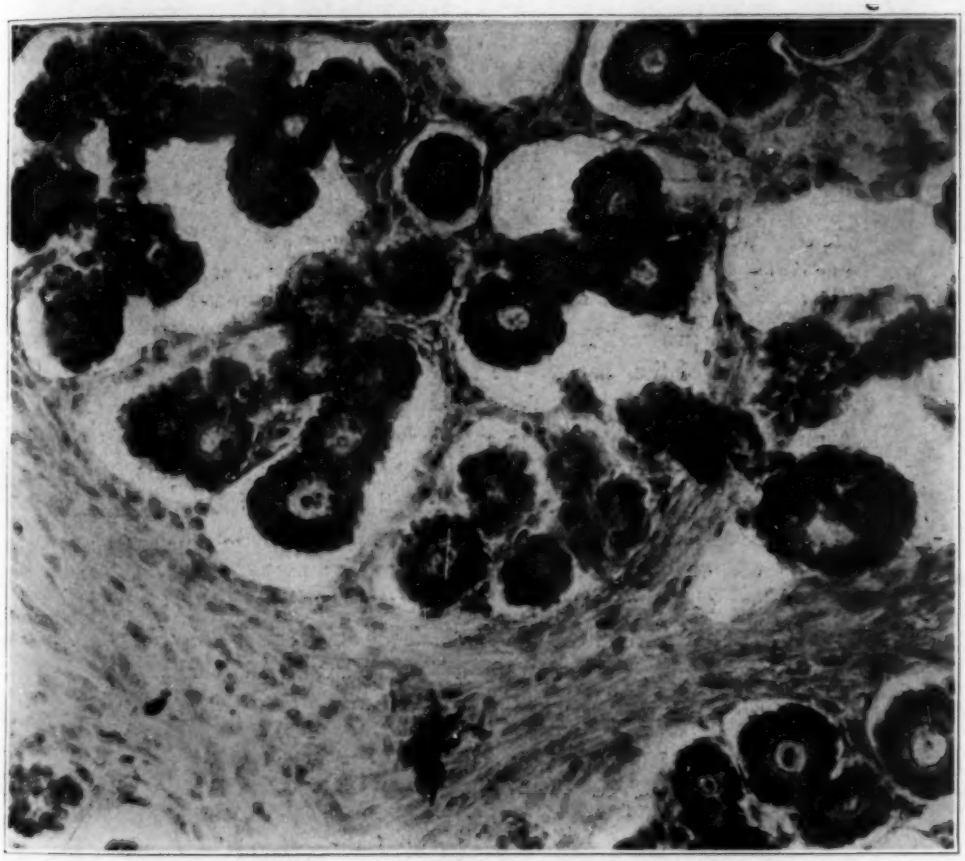

Fig. 2.—Showing rosets under greater magnification; × 500.

tumor as arising from primordial ova of the graafian follicle, because of the large size of the cells, their rounded form, their clear protoplasm, their faintly staining nucleus and nucleolus with a sharp contour, and the fact that there was no cell membrane.

3. Acconci: Centralbl. f. allg. Path. 1890, p. 739.
4. Lonnberg, quoted by Ewing: Nord. med. Ark., 1901.
5. Emanuel: Ztschr. f. Geburtsh. u. Gynäk. **27**:62, 1893.

Gottschalk, who subsequently described a similar tumor, applied the name folliculoma malignum ovarii, and considered the cells found in the center of the roset as primordial ova. Gottschalk's description and illustrations indicate that the histologic structure of the tumor described by him agree closely with the present one, except that in the present instance the acinar-like structure of the neoplasm exists throughout the growth.

The histologic descriptions of the tumors reported by Acconci and Emanuel do not agree with the appearance of the tumor here described, since in their cases the acinar structure was an isolated rather than a dominant part of the tumor architecture. Voigt,[6] who summarized the literature up to 1903, reported a case in which the lesion was bilateral, and called attention to the fact that the central cells could not be considered as primordial ova. The instance reported by Schroeder[7] is also a slightly different type of tumor than the present one.

Ingier,[8] who reported a neoplasm of this type, considered the central cells as degenerating cancer cells, and not as primordial ova, giving as his reason for this belief the fact that while chromosome changes could be demonstrated in primordial ova, such changes were not demonstrable in the central cells of the rosets. He believed the term folliculoma should be discarded and the tumor considered as a carcinoma.

McIlroy[9] believes that the so-called ova are degenerated masses of protoplasm, that they are retrogressive products of the follicle cells which have undergone pseudomucinous and colloid degeneration. Blau,[10] after describing certain hyaline changes occurring in the stroma of a carcinoma of the ovary, called attention to the resemblance of these changes to some of the so-called folliculomas described.

Cases of the folliculoma type have also been described by Meyer,[11] Kahlden,[12] Neumann,[13] and Robinson[14] and discussed by Ewing[15] and Frank.[16]

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6. Voigt: Arch. f. Gynäk. **70**:87, 1903.
7. Schroeder: Arch. f. Gynäk. **64**:193, 1901.
8. Ingier: Arch. f. Gynäk. **83**:545, 1907.
9. McIlroy: J. Obst. & Gynec. Brit. Emp. **10**:331, 1906.
10. Blau: Arch. f. Gynäk. 81:421, 1907.
11. Meyer: Arch. f. Gynäk. **109**:212, 1918.
12. Kahlden: Centralbl. f. Path. **7**:257, 1895.
13. Neumann: Arch. f. Gynäk. **121**:69, 1923.
14. Robinson: Am. J. Obst. & Gynec. **5**:581, 1923.
15. Ewing: Neoplastic Diseases, New York, W. B. Saunders Company, 1922, p. 599.
16. Frank: Gynec. & Obst. Path., New York, D. Appleton & Company, 1922, p. 402.

SUMMARY

A solid tumor of the ovary measuring 18 by 12 cm. was removed from a widow, aged 52, a tripara. Histologic examination showed a large number of roset-like alveoli held together by a stroma composed of spindle cells with relatively long fibrils. In about 30 per cent of the lumina of the rosets polyhedral shaped isolated cells were found, with clear cytoplasm and deeply staining masses of chromatin, apparently nuclei. Usually these cells were free in the lumina.

The tumor belongs to that type described by Gottschalk, and called by him "folliculoma malignum ovarii."

ANEURYSM OF THE ASCENDING AORTA COMMUNICATING WITH THE PULMONARY ARTERY

REPORT OF A CASE *

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CASE REPORT

History.—M. R., a man, colored, aged 48, married, entered the Buffalo General Hospital on April 24, 1925, complaining of shortness of breath and swelling of the feet. From the history it appears that many years ago he had contracted gonorrhea and a genital sore. His present illness dated back about one year. It started acutely with "fever," nausea and vomiting and severe epigastric (?) pain. His physician regarded it as appendicitis, but the patient was not operated on. He remained at home, and soon afterward became dyspneic; his feet and legs began to swell, and the abdomen gradually became distended. Vomiting recurred several times during the first three months of his illness. A cough appeared at frequent intervals, and gradually increasing hoarseness was noticed; the hoarseness was not so marked now, however, as it had been some months before. He had not been able to resume work as a laborer in a car-wheel foundry since about a month after his original attack.

In August, 1924, he entered the Buffalo City Hospital, from which he was discharged improved at the end of October. He reentered the same hospital in January of the following year, with essentially the same symptoms. While there, an almost continuous collection of fluid in the right side of his chest was observed, and considerable quantities were withdrawn on numerous occasions. During the past eight months the patient had spent most of the time in bed whether in the hospital or at home. His general condition had not changed appreciably for several weeks. His best weight was stated as 152 pounds (68.9 Kg.); on entrance it was 110 (49.9 Kg.).

Physical Examination.—The patient appeared as a well developed but poorly nourished colored man, sitting upright in bed by preference, with moderate respiratory distress. Questions were answered slowly and sometimes unintelligibly. There was considerable edema below the knees. Marked arterial pulsations were visible and palpable in the neck and both axillae; the radial pulse was equal in magnitude and synchronous on the two sides, and distinctly collapsing in character—a true water hammer pulse.

Hyperresonance was found over both sides of the chest anteriorly, but posteriorly in the lower half of the right side of the chest there was definite flatness on percussion, the breath sounds much diminished, and vocal fremitus absent. Coarse bubbling râles were heard over the left base posteriorly.

The cardiac impulse was diffuse, and lifted the left chest wall forward with each beat. The apex thrust could be seen and palpated over a considerable area, including the fifth, sixth and seventh interspaces, extending almost to the left

* From the Department of Laboratories, Buffalo General Hospital.

anterior axillary line. In the sixth and seventh interspaces and in the xiphoid region there was a definite systolic retraction not extending laterally beyond the heart border nor visible in the back. The area of cardiac dulness was not increased on the right, but its limit on the left was the anterior axillary line. Extending upward and to the left from the upper left cardiac margin, there was an extra, tongue-shaped process of dulness. A distinct heart shock, diastolic in time, could be felt over the whole precordium, and a thrill, systolic in time, most marked in the second and third interspaces of the left side. A diastolic murmur was heard at its maximum in the aortic area, extending down the sternum and audible over the entire precordium; also, a peculiar and intensely loud, vibratory, systolic murmur, corresponding in time to the thrill, heard best 1 inch to the left of the sternum in the second and third interspaces, and fading out as the apex was approached. A soft systolic brûit was audible posteriorly in the left interscapular region. The pulmonic second sound was accentuated. A tracheal tug was demonstrable with the patient in the upright posture.

The liver margin was smooth, sharp, and extended downward to within an inch of the umbilicus. The spleen was not palpable. No signs of free fluid were present in the abdomen. The superficial lymph nodes, particularly in the axillary, epitrochlear and inguinal regions, were enlarged and hard.

The pupils were equal and regular but did not react to light. The neurologic findings otherwise were not remarkable. The temperature was normal; blood pressure: systolic, 130; diastolic, 60. The urine showed regularly a heavy trace of albumin, and fairly numerous hyaline and granular casts. The Wassermann reaction was ++++. Blood urea nitrogen was 15.4; glucose, 0.108 Gm. Roentgenographically, the heart was found to be enlarged to the left, the aortic arch broadened, pulsating freely. Electrocardiograms showed left ventricular preponderance and arborization block (the patient had been receiving digitalis).

Course of Illness.—The patient improved considerably during his first period in the hospital; the edema disappeared completely, and he was much less dyspneic. He was discharged on July 13. He did not leave his home for three days, during which time he was up and about, even climbing a flight of stairs once. The third day, on his way to the outpatient clinic he ran for the street car, became very weak and dyspneic, was forced to sit down and rest several times on the way, but reached the hospital without assistance. He was readmitted to the ward in about the same condition as on previous admission. Six days later his edema had disappeared. The blood pressure varied between a high average of systolic 130 and diastolic 60 to a low limit of systolic 110 and diastolic 30.

On July 21, a sudden increase in pulse rate occurred from an average of about 80 to 140; this lasted only a short time, however, after an increase in the dosage of digitalis.

On August 8, 250 cc. of blood-tinged fluid were aspirated from the right thoracic cavity.

On October 11, it was noticed that the sclerae of both eyes were jaundiced. The liver margin was now down to the level of the umbilicus and had been, at times, quite tender. Edema of the ankles reappeared, and from this time the patient gradually became weaker and more dyspneic until death occurred on October 23.

Necropsy.—The heart appeared uniformly enlarged; it measured 14 cm. from the apex to the root of the aorta, 10.5 cm. from the left to the right margin, 28 cm.

in circumference at the base, and weighed 540 Gm. The apex was formed by the left ventricle. At the middle of the anterior surface of the right ventricle near the right margin, was a broad fibrous appendage, and on the parietal pericardium in the corresponding location a similar, dense, fibrous thickening; the two apposing surfaces were not adherent.

The aorta and the pulmonary artery seemed to be separated from each other at their origins by a sac bulging prominently forward between them. The

Fig. 1.—Anterior of view of the heart. *R. AN.* indicates the right anterior part of the aneurysmal sac; *L. AN.*, the left posterior part of the sac; *P. A.*, the pulmonary artery.

sac sprang from the aorta to which it was attached by a broad base, and was almost globular, measuring 4.5 by 3.5 cm. in its external diameters.

On opening the pulmonary artery, an oval aperture 1.0 by 0.6 cm. was seen just above the semilunar space of the right segment of the valve, which led into the first named sac. The latter, when the aorta was opened, was revealed as the anterior and right part of an aneurysm of the ascending aorta, measuring

at its origin 3.5 by 3 cm., with its lower margin at about the level of the origin of the coronary arteries. The aneurysm was partly lined with laminated clot and incompletely divided by a vertical septum into two parts, the anterior and right part being the one which communicated with the pulmonary artery, the posterior and left part, the one mentioned as bulging between the pulmonary artery and the left auricular appendix. The right ventricle was somewhat dilated; its wall measured 0.7 cm. in its thickest part. The left ventricle also appeared somewhat dilated; its wall measured 1.7 cm. in thickness. The aortic ring was 8.5 cm. in circumference. All the valves appeared competent, not retracted, though moderately thickened, especially the aortic valves. The heart muscle was brownish red. The coronary arteries showed a moderate degree of arteriosclerosis. The aorta beyond the aneurysm showed closely set, small, irregular, yellow, arteriosclerotic plaques.

Fig. 2.—Right ventricle and pulmonary artery opened, showing the perforation.

The right pleural cavity contained a small amount of blood-tinged fluid. A few thick, fibrous bands attached the upper lobe of the left lung to the parietal pleura.

The left lung was crepitant throughout, though uniformly increased in density, its surface smooth except in the apex, which was moderately scarred and contracted. At its base posteriorly, the lung substance was boggy, and from its cut surface considerable fluid could be expressed.

The apex of the right lung was similarly contracted. At the lower portion of the upper lobe, a firm, irregularly lobulated mass could be palpated, which on separating the lobes, became visible, projecting downward from the surrounding lung tissue. Its cut surface was brownish red, granular and airless,

and projected well above the surrounding tissue. The aerated portions of both lungs were dull grayish brown, uniformly increased in density and heavily mottled with anthracotic pigment.

The surface of the stomach showed on its lesser curvature about 2 cm. from the pyloric ring a shallow, indurated ulcer, measuring 0.8 by 2 cm., with a raised, rounded margin and rough, scarred base.

The liver weighed 980 Gm.; its surface was smooth, its color reddish brown. At the lower surface it showed a network of congested vessels. The cut surface showed exaggerated markings, the centers of the lobules appeared sunken and deep red, the peripheries grayish yellow and raised. The dilated sinuses were prominent in the lower half of the right lobe, and appeared as a coarse, black network through its substance.

Fig. 3.—Left ventricle and aorta opened, showing the right and left parts of the aneurysmal sac, the septum between them, and the aperture in the right sac communicating with the pulmonary artery.

The kidneys weighed together 560 Gm., were of approximately equal size, and the capsules stripped easily, leaving a finely granular surface with a fine network of stellate veins. The relative widths of cortex and medulla bore to each other the normal ratio.

Histologically, sections from the aorta adjacent to the aneurysm showed pictures representing a combination of arteriosclerosis with syphilitic mesaortitis. The intima consisted of a hyalinized, sclerotic membrane of irregular thickness showing only here and there remnants of the external elastic lamella. Fibrous processes from the intima in many parts invaded the middle coat.

interrupting its continuity in many places. Toward the outer surface, the media seemed well preserved while the adventitia was thickened to several times its normal size, consisting throughout of a chronic granulation tissue with here and there areas of small cell infiltration of considerable size. The appearance of the granulation tissue was especially prominent toward its inner border and in places continued on to the media.

Anatomic Diagnosis.—The diagnosis was: syphilitic mesa-ortitis combined with arteriosclerosis; bilocular aneurysm of the ascending aorta communicating by a small aperture with the pulmonary artery just above the valve; moderate excentric hypertrophy of the heart with predominant dilatation of the right ventricle; brown induration of the lungs; chronic passive congestion of the liver, with localized fibrosis; chronic passive congestion of the spleen and kidneys; lobular pneumonia of the right lung; chronic adhesive pleuritis of the left lung; healed peptic ulcer in the pyloric region of the stomach.

COMMENT

In view of the anatomic features of the aneurysm, the histologic changes in the wall of the aorta and the clinical and serologic evidence of syphilis in the case, there can be no doubt that we are dealing with the usual type of aneurysm occurring in that location based on syphilitic alteration of the aorta. This is emphasized in order to exclude from consideration a smaller type of aneurysm rarely occurring in this region and likely to perforate into the pulmonary circulation, which is not based on syphilis. From a recent study of this subject by Abbott,[1] this type of aneurysm appears to depend on a developmental defect.

There can also be little doubt that the communication between the aneurysm and the pulmonary artery is the result of perforation of the former into the latter. The aneurysm was clearly a part of the aorta; there was no dilatation of the pulmonary artery, nor did that vessel appear diseased in the region of the perforation.

As to the time of rupture, while its definite determination is impossible, the evidence seems sufficient to assume that it had taken place about one year prior to the patient's death. It would seem to coincide with his attack of epigastric pain, which was associated with dyspnea. It was only then that symptoms of cardiac failure began to develop, becoming progressively worse. Moreover, since that time there seems to have been no other sudden, acute disturbance of the circulation which might correspond with such an insult.

Although this case is reported chiefly as a pathologico-anatomic rarity, the problem offered in diagnosis by the physical signs may be of interest. The most striking of the physical signs was the peculiar, harsh, systolic murmur heard at the base and diminishing in intensity toward the apex.

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1. Abbott, Maude E.: Contrib. to Med. & Biol. Res. **2**:899, 1919.

This murmur associated with accentuated pulmonic second sound suggested to the clinicians the possibility of a patent ductus arteriosus. This, however, was untenable because of the total absence of cardiac symptoms in childhoood and the age of the patient. Therefore the murmur was rather assumed to be connected in some way with the aneurysm, the presence of which was recognized. With the thought of patent ductus arteriosus the communication between the aortic and pulmonary circulation evidently was recognized, but, possibly because of its rare occurrence, the perforation of the aneurysm into the pulmonary artery was not considered.

The subject of aortic aneurysm perforating into the pulmonary artery has recently been reviewed by Scott,[2] and the various clinical and anatomic features summarized on the basis of twenty well studied cases, including two of his own. From the reviews given by this author, Kappis,[3] Stevenson,[4] Jankovich,[5] and Peacock,[6] it is safe to estimate the entire number of cases reported to date as between forty and fifty. It seems that most of the cases reported differed little in their clinical features, and, according to Scott, the peculiar harsh systolic murmur accompanied by a thrill, as in our case, was a common feature. Anatomically, variations were noted in the size and shape of the aneurysm, the location of the perforation, its size and age. In most cases, however, there was a sacculated aneurysm at the root of the aorta involving the sinuses of Valsalva or located immediately above them (Scott). It should, perhaps, be emphasized that, in contradistinction to the already mentioned congenital aneurysms which tend to perforate below the pulmonary leaflets into the right ventricle, this type of aneurysm mostly perforates above the leaflets into the vessel proper.

The unusual feature in the case seems to be the comparatively long survival of the patient after the perforation, providing the assumption is correct that perforation had taken place about a year prior to his death. Certainly the anatomic appearance of the perforation did not contradict this assumption.

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2. Scott, R. W.: Aortic Aneurysm Rupturing into the Pulmonary Artery, J. A. M. A. **82**:1417 (May 3) 1924.
3. Kappis, M.: Deutsch. Arch. f. klin. Med. **90**:506, 1907.
4. Stevenson, H. N.: Bull. Johns Hopkins Hosp. **24**:217, 1913.
5. Jankovich, L.: Wien. klin. Wchnschr. **31**:73, 1918.
6. Peacock, W. E.: Lancet **1**:767, 1920.

CARCINOMA OF THE THYMUS

AND OCCLUSION OF THE SUPERIOR VENA CAVA *

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Judging from the literature on carcinoma of the thymus and thymic neoplasms in general, one can definitely conclude that the pathogenesis of these tumors is very much unsettled. One of the primary reasons for this situation is, undoubtedly, the lack of agreement concerning the histogenesis and structure of the thymus.

Practically all authorities are agreed that the thymus in mammals is originally epithelial, arising from the third and fourth branchial clefts. It is also generally believed that the reticulum and the concentric epithelial bodies or corpuscles are epithelial structures which arise from the epithelial anlage. These conclusions are based on sound embryologic data.

Regarding the origin and nature of the small round cells of the thymus, there is still much confusion. Many are familiar with the views of Stöhr, Pappenheimer [1] and others, who believe that the small round cells of the thymus are epithelial cells. Pappenheimer's work may be criticized because no early embryos were studied, since it is well known that the cells in question put in their appearance early in fetal life. On the other hand, Hammar,[2] Maximow and the more recent writers regard the small round cells of the thymus as lymphocytes which have migrated into, proliferated among, and separated, the epithelial cells of the thymus. Badertscher,[3] in 1914-1915, as a result of an extensive embryologic study, apparently rightly concluded that the small round cells of the thymus were lymphocytes which had infiltrated and then proliferated in the thymus, thereby becoming a part of that organ. In 1916, Vera Danchakoff,[4] using embryonic material, reached essentially the same conclusions. Hammar, in 1922, in summarizing

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* From William H. Singer Memorial Research Laboratory and Allegheny General Hospital.

1. Pappenheimer, A. M.: A Contribution to the Normal and Pathological Histology of the Thymus Gland, J. Med. Res. **22**:1, 1910.

2. Hammar, J. A.: The New Views as to the Morphology of the Thymus Gland and Their Bearing on the Problem of Function of the Thymus, Endocrinology **5**:731, 1921.

3. Badertscher, J. A.: The Development of the Thymus in the Pig, Am. J. Anat. **17**:317, 1914-1915; The Development of the Thymus in the Pig, ibid., p. 437.

4. Danchakoff, V.: The Differentiation of Cells as a Criterion for Cell Differentiation, Considered in Relation to the Small Cortical Cells of the Thymus, J. Exper. Med. **24**:87, 1916.

our newer knowledge concerning the morphology and the function of the thymus, finds the predominance of evidence in favor of the lymphoid nature of the small round cells of the thymus.

Apparently the thymus is a mixed organ, composed mainly of lymphoid and epithelial cells. At the same time one must remember that the thymus is otherwise histologically unlike a lymph node. There are no lymph sinuses nor lymph follicles, while eosinophilic cells and other elements may be present. The thymus seldom shows changes parallel with the primary diseases of the lymphoid tissue except, perhaps, in status thymicolymphaticus.

The peculiar cycle of the thymus involves, among other features, marked regressive changes after puberty. There may be, however, a persistance of both epithelial structures and lymphocytes well into middle life and later. Numerous instances of the persistent thymus are to be found in the literature, and in his last paper, Hammar emphasizes the presence of the thymus in the seventh and eighth decades. I have, on several occasions, observed microscopic remnants of the thymus in persons of middle life, especially in one woman aged 53, and recently in a man aged 74. The reticular epithelium of the thymus in the case of this woman showed a moderate hyperplasia. The possibility of epithelial as well as other tumors arising from the thymus in the later years of life is, therefore, obvious.

Ewing,[5] in 1916, while accepting the epithelial nature of the thymic reticulum, derived lymphosarcoma or thymoma and also carcinoma from the reticulum. In 1922, in his book on tumors,[6] he still maintains the same views.

ABSTRACTS OF CASES

I have reviewed the literature on the subject, and I have found fifteen apparently authentic cases of carcinoma of the thymus, besides certain incomplete and other doubtful cases referred to below. Two incompletely abstracted Japanese cases were found, which perhaps should bring the total to seventeen. Only three of these cases are found in the American literature, and eight of them are reported by the French. My case seems to be the fourth American one. Rubaschow, in 1911, compiled a list of twelve cases of carcinoma of the thymus, but the early cases, on careful study, are found to be more or less doubtful.

The first case, regarded by many as carcinoma of the thymus, was described by Bristowe[7] in 1854, in a man, aged 22. It is possible that

5. Ewing, J.: The Thymus and Its Tumor, Surg. Gynec. & Obst. **22**:461, 1916.

6. Ewing, J.: Neoplastic Diseases, ed. 2, New York, W. B. Saunders Company, 1922, p. 912.

7. Bristowe: Cancer of the Kidneys, Upon the Pleura and Mediastina, Tr. Path. Soc. London **5**:185, 1854.

his case was a carcinoma; however, one cannot be certain, because descriptive details are not clear. Bristowe makes no mention of the thymus, yet the tumor, no doubt, was a malignant thymic neoplasm.

Certain writers list Erichsen's [8] case, which was published in 1867, as the second reported carcinoma of the thymus. The patient was 23 years of age, and gave classical symptoms and signs of a mediastinal growth. The tumor was unusually large, lobular and partially cystic. Because of the absence of microscopic description, one is left in doubt as to the exact nature of the neoplasm. Erichsen considered it a medullary carcinoma, but he gives nothing to support his opinion. It probably was also a malignant thymic neoplasm, but its carcinomatous nature is questionable.

Cayley,[9] in 1868, reported apparently the first carcinoma of the thymus, in a woman aged 56. The patient had a cough, swelling in the left side of the neck and above the clavicles, edema of the left upper extremity, and pleural effusion. Necropsy revealed a fair sized, firm, nodular tumor in the upper anterior mediastinum. The growth had surrounded and compressed the left innominate vein, and the left subclavian and left jugular veins were plugged by thrombi. Secondary growths involved the tracheobronchial mediastinal and clavical lymph nodes, pleura and lung. Microscopic remnants of the thymus were found in the neoplasm.

In 1890, Letulle [10] reported eight cases of mediastinal neoplasms, the last two of which were probably carcinomatous. In both cases of carcinoma there were symptoms of a mediastinal tumor, which among other things gave signs of obstruction of the superior vena cava. His seventh case, the first carcinoma case in the series, was that of a woman, aged 23. His eighth case was the second one of carcinoma in a man, aged 65. The large mediastinal tumor in each case enveloped the mediastinal vessels and involved the thoracic lymph nodes. At necropsy, the superior vena cava was found completely obliterated in the first case, and almost so in the second one. Both cases are described histologically as epithelial tumors. He does not state the thymic origin of the last case, but apparently he so considered it. The second case presented a scirrhous type of growth.

Dansac,[11] in 1893, found a retrosternoclavicular mass in a man, aged 55. The patient was cachectic and complained of weakness, cervical

8. Erichsen: Fall von Carcinom des vorderen Mediastinum, Jahresb. ü. d. Leistung. i. d. ges. Med. **1**:292, 1867.

9. Cayley: Cancer of the Anterior Mediastinum Probably Originating in the Thymus Gland, Tr. Path. Soc. London **19**:53, 1868.

10. Letulle, M.: Thymus et tumeurs malignes promitives du mediastin anterieur, Arch. gén. de méd. **20**:64, 1890.

11. Dansac, M.: Cancer du thymus, du poumon et du foie, etc., Bull. Soc. anat. de Paris **7**:140, 1893; Examen histologique d'un cancer primitif du thymus avec cancer primitif du foie, Bull. Soc. anat. de Paris **7**:199, 1893.

pain and changes in his voice. There was paralysis of the left vocal cord. At necropsy, a large mediastinal tumor extended upward almost to the thyroid gland. The tumor, structurally, was a large cell carcinoma with much connective tissue and many eosinophilic cells. Concentric epithelial corpuscles were found only in the upper portion of the tumor. Lymphoid infiltration was a feature especially about the vessels. Dansac considered the tumor masses in the liver a primary cylindrical cell carcinoma, and he regarded the pulmonary nodule as a secondary growth from the hepatic carcinoma. Descriptive details regarding the hepatic and pulmonary masses are meager, and it is possible that they were metastases from the thymic carcinoma.

For his thesis, Ambrosini,[12] in 1894, described one case of carcinoma of the thymus, and referred to three cases in Letulle's paper. The case of Letulle, designated as case 3 by Ambrosini, cannot be regarded as carcinomatous on the basis of the description given by Letulle. Ambrosini's case was that of a man, aged 52, who presented signs of a mediastinal growth and edema of the lower half of the body. A large, hard and fibrous anterior mediastinal tumor was found at necropsy. It had involved the lungs and also invaded the pericardium and had produced a sanguineous pericardial effusion. Structurally the tumor was a carcinoma, essentially scirrhous in type.

In October, 1894, Vermorel and Thiroloix [13] published Ambrosini's case which had appeared in the latter's thesis in June of that year. These writers made no mention of Ambrosini's thesis, and they should not be credited with this case.

The next case was published in 1896 by Paviot and Gerest.[14] Their patient was a woman, aged 52. She complained of change in her voice, cough, thoracic pain, cyanosis, dyspnea and edema in the legs. A large mass was found about the sternum and clavicles, and the veins of the thorax were dilated. The lymph nodes above and below the clavicles, and those of the neck, were involved. Physical signs were those of a thoracic growth which was found at postmortem examination. The large tumor mass was hard and occupied the position of the thymus. There were also a pericardial effusion and a metastatic nodule in the renal capsule. There was described an epithelial tumor with giant cells and spherical bodies formed by the tumor cells.

Eisenstädt,[15] in 1902, presented the case of a man, 28 years of age, who complained of suffocation, and who had evidences of obstruction

12. Ambrosini, G.: De l'epithelioma du thymus, Thèse de Paris, 1894.

13. Vermorel and Thiroloix, J.: Epithelioma pavimeuteux lobulé a globes epidermiques a point de depart thymique, Bull. Soc. anat. de Paris **69**:702, 1894.

14. Paviot, J., and Gerest: Un cas d'epithelioma primitif du thymus, Arch. de méd. expér. **8**:606, 1896.

15. Eisenstädt, J.: Ueber Krebes der Thymus, Inaugural Dissertation, Greifswald, 1902.

of the superior vena cava. The physical findings indicated a mediastinal mass. A large mediastinal tumor was found postmortem, which occupied the position of the thymus and had involved both lungs and the pericardium. Metastases were found under the clavicles, in the thoracic wall and elsewhere in the thorax. The trachea was compressed, but the superior vena cava was not mentioned. The sections revealed an epithelial neoplasm with giant cells and much fibrous tissue.

Burch's [16] case was reported in 1904. The patient was a man, 39 years old, who complained of dyspnea, dysphagia, exophthalmos, edema and dilated veins of the neck. A large mediastinal tumor mass was found which extended from the base of the neck to the heart. It was adherent to the vertebrae and surrounded the mediastinal vessels, the trachea and the esophagus. The trachea was compressed. The microscopic details are brief, but he regarded the growth as a thymic carcinoma.

The case detailed by Thiroloix and Debré [17] was that of a man 56 years of age. Their patient presented symptoms of a mediastinal tumor with hard nodules on the thorax anteriorly, and a mass arising from behind the sternum and extending into the neck. The large pyramidal and adherent tumor of the anterior mediastinum had invaded the pericardium. Histologically, they described a carcinoma undergoing keratinization, with multinucleated giant cells and much fibrous tissue. Epithelial bodies resembling the epithelial bodies of the thymus are illustrated and described.

Achard and Paisseau,[18] in 1908, described a large mediastinal tumor, considered thymic in origin, in a man 71 years of age. The tumor involved the thyroid gland and reached to the base of the heart. The superior vena cava surrounded by the mass was occluded by a thrombus. A small renal metastasis was discovered. From the text and the illustrations, the tumor resembles, somewhat, an epidermoid carcinoma, and apparently it is similar in this respect to the case of Strauss.[19]

Simmond's [20] case, in 1912, occurred in a man 30 years of age, who complained of edema of the face and dyspnea. The mediastinal tumor constricted the superior vena cava and trachea. Metastases were found in the thoracic lymph nodes and lungs. The tumor was an epithelial

16. Burch: Tumeur maligne du mediastin ayant probablement comme point de depart un vestige de thymus, Progrès méd. **19**:267, 1904.

17. Thiroloix, J., and Debré, R.: A propos d'un epithelioma du mediastin anterieur, Arch de méd. exper. et d'anat. path. **19**:668, 1907.

18. Achard, C., and Paisseau, G.: Epithelioma thymique de la region thyroidienne, Arch. de méd. expér. et d'anat. path. **20**:78, 1908.

19. Strauss, S. G.: Malignant Neoplasm of the Thymus, New York M. J. **110**:646, 1919.

20. Simmonds, M.: Ueber maligne Thymusgeschwülste, Ztschr. f. Krebsforsch. **12**:280, 1912-1913.

one with much fibrous tissue and many infiltrated small round cells. His description is meager, but the growth appeared to be a carcinoma.

In 1919, Strauss [19] reported a case of carcinoma of the thymus in a man 60 years of age. The tumor in this instance had obliterated the superior vena cava and had also invaded the myocardium. The postmortem examination was incomplete, but the sections of the tumor were unmistakably carcinomatous, resembling an epidermoid carcinoma.

Sotgia's [21] case appeared in 1919 in a man 45 years old. In the anterior mediastinum occupying the position of the thymus was a large, hard and adherent tumor, which had involved the adjacent lymph nodes. The neoplasm was a carcinoma and contained much fibrous tissue. Epithelial bodies were present. He considers his case as the fifth reported carcinoma of the thymus.

The case detailed by Symmers and Vance [22] in 1921 was that of a man 58 years old, who complained of dysphagia and pain in the back. He later developed symptoms of a transverse myelitis. At the postmortem examination a large tumor was found occupying the position of the thymus, together with metastases in the lungs, vertebrae and spinal dura. The spinal cord was compressed. The cells of this carcinoma were both large and small. Whorls of cells were found, suggesting perhaps the concentric thymic epithelial bodies. There was also evidence of keratinization by the neoplastic epithelium.

Jacobson's [23] case was that of a man 42 years old, who consulted his physician because of pain in his back. Attention was first focused on the spinal metastasis, with evidence of involvement of the meninges, but later the roentgen ray revealed mediastinal and pulmonary growths. At necropsy, a fair sized cystic thymic tumor was found, together with secondary tumors in the lungs, liver, vertebrae, suprarenal glands and in the lymph nodes of the thorax and retroperitoneum. Jacobson regards this as a case of thymic carcinoma arising from the epithelium of the concentric corpuscles. The cysts and widespread metastases constituted distinctive features.

Recently Kneringer and Priesel [24] have described a case of a malignant tumor of the thymus as a mixed epithelial and lymphoid neoplasm. From the description and the illustrations, the tumor is undoubtedly and primarily epithelial. The patient was a man 71 years old, who had had

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21. Sotgia, G. M.: Un carcinoma primitivo del timo, Arch. per le sc. med. **42**:69, 1919.

22. Symmers, D., and Vance, B. M.: Epitheliomata of Thymic Origin, Arch. Int. Med. **28**:239 (Sept.) 1921.

23. Jacobson, V. C.: Primary Carcinoma of Thymus, Arch. Int. Med. **31**:847 (June) 1923.

24. Kneringer, E., and Priesel, A.: Ein Beitrag zur Kenntnis der Thymome (Lymphoepithelioma thymi), Virchows Arch. f. path. Anat. **241**:475, 1923.

symptoms for seven or eight years. Tuberculosis was a complicating factor and involved the pleura. In view of these facts, especially the presence of long standing tuberculosis, it is not surprising to have found small lymphoid cells in large numbers. The absence of diffuse proliferation in these cells and the fact that they were small lymphocytes is also in favor of their inflammatory origin. Lymphocytic infiltration and even newly formed lymph follicles in and about a slow growing carcinoma, are not uncommon. The neoplastic rôle of the lymphocytes in this tumor, seems, therefore, open to question. The tumor is probably a carcinoma.

Honda and Taguchi [25] refer to two cases of carcinoma of the thymus in the Japanese literature, but their abstracts are so brief as to be of little value.

Sweany's [26] case was perhaps a carcinoma of the thymus, but the data given are incomplete, so that it warrants no special classification.

Rubaschow's [27] case was a mixed tumor composed mostly of lymphocytes, according to the illustrations and the description. It should not be considered among the carcinomas of the thymus.

Meriel and Tourneux [28] described a cervical tumor, which they considered of thymic origin. Aberrant thymic tissue does occur in the neck, but such tissue was not found in their case. They offer little in support of the thymic origin, aside from the theoretical possibility.

In this connection it is perhaps well to refer to the case of Foot and Harrington.[29] The patient was an infant with a large mediastinal neoplasm. The authors regarded the tumor as an epithelial thymic tumor arising from the anlage of the thymus. At the same time the thymus itself was negative both grossly and microscopically. The thymic origin of this neoplasm cannot be regarded as proved.

REPORT OF A CASE

History.—Andrew Z., a white man, aged 35, was admitted to the Allegheny General Hospital, Dec. 19, 1924, on the medical service of the late Dr. J. C. Ohail, and died of an acute hemorrhage Jan. 25, 1925. His past history was unimportant.

His chief complaint was pain in the chest. The illness apparently started about six weeks previous to admission, with a slight hemoptysis. Later he grew weak,

25. Honda, I., and Taguchi, K.: Ueber primäre basartige geschwülste des Thymus, Gann. **15**:57, 1921.

26. Sweany, H. C.: Primary Tumor of Thymus Associated with Tuberculosis, J. A. M. A. **80**:754, 1923.

27. Rubaschow, S.: Ein bäsartige Thymusgeschwülst, Virchows Arch. f. path. Anat. **206**:141, 1911.

28 Meriel and Tourneux, J. P.: Epithelioma cervicale développé dans un lobule thymique aberrant, Bull. et mém. Soc. anat. de Paris **92**:180, 1922.

29. Foot, N. C., and Harrington, H.: Malignant Epithelial Thymoma, Am. J. Dis. Child. **26**:164, 1923.

and a cough developed, together with severe and continuous pain deep in the middle of his chest. Expectoration soon became abundant. Shortly before admission he also complained of a sense of oppression in the epigastrium, but there was no mention of such a feeling in the thorax.

Physical Examination.—The patient was a well developed but somewhat emaciated white man. He had a frequent and productive cough, but the cough did not seem to be accompanied by an exacerbation of the pain. The head and neck presented a slight suffusion, and the superficial veins were dilated. The thorax was emphysematous in type, but otherwise negative to inspection. The lungs presented signs at both apexes, but especially on the right, which were interpreted as those of rather advanced pulmonary tuberculosis. The heart and vessels were negative. The blood pressure was 102 systolic and 74 diastolic. The abdomen was normal as were also the external genitalia. The fingers were swollen and cyanotic, but the upper extremities were not described as edematous. The lower extremities were normal. The deep and superficial reflexes were present and active. No enlargement of the superficial lymph nodes was observed.

Laboratory Findings.—Several urine examinations were negative, with the exception of a trace of albumin and occasional hyaline casts. On January 17, blood examination revealed: red blood cells, 4,088,000; white blood cells, 20,100; hemoglobin, 80 per cent. (Sahli); differential count, 250 cells counted; polymorphonuclears, 77.6 per cent; polymorphonuclear basophils, 0.4 per cent; polymorphonuclear eosinophils, 0.4 per cent; lymphocytes, 16.4; large mononuclears and transitionals, 4.8 per cent.; myelocytes, 0.4 per cent. Examination on December 20 revealed: nonprotein nitrogen 30 mg. and sugar 111 mg. per hundred cubic centimeters of blood; January 10: nonprotein nitrogen, 25 mg. and sugar 123 mg. per hundred cubic centimeters of blood. On December 20, 21, and January 20, the sputum was negative for tubercle bacilli.

On January 22, the roentgen ray revealed a large and dense mediastinal shadow posterior and to the right of the aortic arch and also extending into the right lung. It was considered a new growth.

Course of Illness.—On January 2, notwithstanding the absence of tubercle bacilli in the sputum, the patient was regarded as suffering from advanced pulmonary tuberculosis, especially in the right lung.

The swelling of the neck, the face, the eyelids and the upper thorax was well marked on January 18, and the superficial vessels of the chest became noticeably dilated, as were also those of the neck. The arms were not especially edematous. Pain in the chest and right shoulder continued to be severe.

By January 23, in addition to the presence of dilated veins of the neck and chest, dilated veins of the abdomen were noticeable. The sputum contained a fair amount of blood. For the last few weeks the patient complained of pain in the epigastrium.

The patient died, January 25, of a massive hemoptysis.

The temperature was, on the whole, within normal limits, until January 12, the twenty-fifth day in the hospital, when there was an elevation to 100 F. The temperature remained irregularly elevated, 100 to 101 F., until death. The pulse rate was accelerated throughout, averaging 100 to 110 per minute. The respirations were slightly increased in rate ranging from 24 to 28 per minute.

Necropsy.—I performed the necropsy forty-two hours after death.

The body was that of a large, middle aged, white man, well developed but emaciated. The head, the neck, the upper half of the thorax and the upper extremities were moderately edematous. The edema was especially well marked in the face and neck. The eyelids were greatly swollen. The superficial vessels

of the neck, however, were identified with difficulty, while none were found over the thorax, abdomen, arms or face. The thorax was markedly emphysematous. The scrotum was edematous.

On opening into the peritoneal cavity, the liver was found 9 cm. below the costal margin on the right side and well below the costal margin on the left. The organ was adherent to the lower edge of the diaphragm on the right side, over an area about 10 cm. in diameter. The diaphragm was unusually low on each side. About the appendix there was evidence of a previous healed inflammation. The retroperitoneal lymph nodes were moderately enlarged, firm and gray.

The superior anterior mediastinum contained a huge and hard tumor mass adherent to the sternum, which occupied the position of the thymus. The mass extended from the base of the heart high into the neck. It had almost ascended to the thyroid gland in the midline and on the left side, while it reached the lower border of the thyroid cartilage on the right. The mass extended deep into the mediastinum and involved the large vessels, and was fixed for the most part. The greater portion of the mass was to the right of the midline. The lungs were adherent to the mass, especially the upper lobe of the right lung into which the tumor had extended.

The pericardium was moderately edematous and contained from 100 to 150 cc. of turbid fluid with flakes of floating fibrin. The parietal and visceral surfaces of the pericardium were dull; the small vessels were numerous and dilated. The heart was lying free and contracted. About the intrapericardial portion of the superior vena cava was found a large, hard and nodular mass, pinkish and gray, projecting into the pericardial cavity. The growth also completely filled the intrapericardial portion of the superior vena cava. The tumor was densely adherent and invaded the pericardium about the base of the heart, and completely surrounded the aortic arch and the extrapericardial portion of the pulmonary artery and its two branches.

The lungs were voluminous, and the pleural cavities were unusually large. The right lung, as stated above, was invaded by the growth medially in its upper half and was also densely adherent laterally, posteriorly and to the diaphragm. A large collection of encapsulated turbid fluid, approximately 500 cc., was found laterally in the right pleural cavity. The left lung was everywhere densely adherent, except anteriorly.

The azygos vein and its tributaries were not dilated. The azygos vein entered the superior vena cava, but the mouth of the former vessel was closed by the tumor which filled the vena cava. The azygos vein contained no thrombus. For certain reasons the superficial cervical and trunk veins were not dissected.

The tumor mass was roughly pyramidal in shape and measured approximately 11 by 8 cm. Its greatest diameter was the transverse one, just over and above the aortic arch. The surfaces were irregular and somewhat nodular and were partially covered by yellow adipose tissue.

On the left side the aortic arch was found embedded in the mass. The three large arteries which arise from the aorta were also embedded in the mass and somewhat distorted, though not greatly narrowed. The subclavian and the internal jugular veins of the right side were seen projecting from the mass and completely thrombosed. How far laterally the subclavian thrombosis extended was not determined, but it was at least a few centimeters. The left jugular vein was also thrombosed. The thrombosis in each jugular vein extended upward on either side of the thyroid gland. The stump of the left subclavian vein was not occluded, but the vessel was small.

Posteriorly the trachea was almost surrounded by the mass, but not compressed. The esophagus was uninvolved.

On the right lateral side of the tumor, and also posteriorly, there was a large necrotic area which involved the right primary bronchus and the right pulmonary artery. The bronchus was largely necrotic from its bifurcation downward for about 2 to 3 cm. The overlying right pulmonary artery, also partially necrotic, had ruptured into the right primary bronchus. The primary bronchi, trachea and larynx contained a cast of clotted blood.

On section of the tumor at right angles to the trachea, it was found to be made up mostly of irregular patches of firm, gray and dry tissue, much of which was necrotic. The more peripheral tissues were much better preserved, especially anteriorly. The tumor was not altogether homogeneous, because of the incorporated tracheobronchial lymph nodes, which were enlarged and anthracotic. The outlines of the lymph nodes were not sharp, and they could not have been recognized except for the pigmentation. A fair amount of yellowish adipose tissue was found superficially in the anterior portion of the mass. There were no hemorrhages in the tumor.

The innominate veins and the superior vena cava were completely occluded, the latter by tumor growth and the former by an organized thrombus. Much of the tumor tissue filling the vena cava was necrotic but that adjacent to the projecting pericardial nodules was firm and friable. The organized thrombi of the innominate veins was continuous with the thrombi of the internal jugular veins, but the thrombus did not enter the mouth of the right subclavian vein, which was lying within the tumor. The innominate, subclavian and carotid arteries, though embedded in the tumor and somewhat narrowed and distorted, all had a smooth intima.

The greatly enlarged and anthracotic lymph nodes lying between the bifurcation of the bronchi at the base of the tumor were practically replaced by tumor tissue, but a few partially calcified tubercles were easily identified.

The heart weighed 350 Gm. The organ was normal in shape and configuration, and partially contracted. Aside from the evidence of pericarditis, it was normal externally. The chambers, myocardium and the coronary vessels presented nothing of importance.

The right lung weighed 960 Gm.; the left lung weighed 748 Gm. The right lung was large and voluminous. A large, irregular and superficial softened mass of gray tumor tissue was found involving the median aspect of the upper lobe, where it had been adherent to the tumor. Other smaller masses were found in the depths of the lung posteriorly. The hilic lymph nodes were not unlike those found between the primary bronchi, but tubercles were absent. The lung was extensively anthracotic and the surfaces ragged. On section, the tumor tissue was found limited to the upper lobe, but in places it appeared to have followed the bronchial tree for some distance into the lung. The deep-seated nodules on section were hemorrhagic and rather soft and different in appearance from the gray tumor tissue in the upper lobe. The lung tissue was soggy and dark, and bronchopneumonia could not be demonstrated.

The left lung, with the exception of a slight hilic infiltration by the tumor, was not unlike its fellow. No deep-seated tumor masses were found, but soft hemorrhagic patches, as found in the right lung, were scattered about. The hilic lymph nodes were essentially the same as those of the right lung.

The right kidney weighed 280 Gm.; the left kidney, 310 Gm. The right kidney was large. On the anterior surface of the upper pole, a small projecting and light yellow tumor was found. The tumor was soft and roughly triangular

in shape and extended almost to the hilum. On the cut surfaces it measured 2.5 by 1.5 cm. The tumor was spongy, sharply circumscribed and coarse in texture, and suggestive of a hypernephroma. In the lower pole of this kidney a second and smaller but deeply embedded tumor was discovered. This tumor was sharply circumscribed, firm and gray. It measured 12 by 15 mm. This body was regarded as a probable metastatic nodule from the mediastinal neoplasm. Otherwise this kidney was not unusual.

The left kidney was very large, and it presented a fair sized cystic structure projecting from the midanterior surface. This cyst measured 2.5 by 2.5 cm. It contained clear fluid and was made up of several compartments. There was no solid or spongy yellowish tissue in the deeper walls of this multilocular cyst, which was sharply defined. Otherwise this kidney was like its fellow.

The thyroid gland was moderately enlarged and homogeneous, and presented the typical gross appearance of a colloid goiter.

The liver, the pancreas, the spleen, the urinary bladder and the ureters, the suprarenal glands, the gastro-intestinal tract, the testicles and the brain were normal. No other metastases were found.

Microscopic Examination.—Zenker's fluid was used for a fixative and methylene blue and eosin for staining.

The tumor tissue was fairly well preserved so far as postmortem changes were concerned. It presented two contrasting types of carcinomatous growth, a diffuse and cellular neoplasm on the one hand, and a scirrhous type on the other. The former appeared to predominate. Large and small patches of necrosis involved much of the tumor, and here and there were a few small hemorrhages and fibrin deposits. Invasion of the lymphatics was a noteworthy feature, as well as invasion of certain of the small veins.

In the more cellular areas the carcinoma cells were irregular in size and shape, but relatively large and for the most part flat. The cytoplasm was moderate in amount, basophilic and generally deeply stained. The nuclei were oval, round and vesicular, with from one to three nucleoli. A fair number of hyperchromatic nuclei and irregular mitotic figures were found. The nuclei in many cells were eccentrically placed. Tumor giant cells were fairly numerous, and also clumps of cells so closely packed as to give the appearance of giant cells. Certain giant cells were multinucleated, but most of them had a single, very large, lobulated or oval vesicular nucleus. Many of the giant cells appeared to have surrounded smaller cells. A few of the included or surrounded cells had undergone necrosis, while others of the giant cells showed degeneration of their own cytoplasm. Mitoses among the giant cells were numerous and irregular.

In a few areas unmistakable patches of thymic tissue were found in the midst of the more cellular portions of the neoplasm. Occasional well formed and normal concentric epithelial bodies or corpuscles, characteristic of the thymus, were observed. The appearance of such patches strongly suggest an origin of the tumor from the reticulum of the thymus, as the carcinoma cells in places formed long strands of flattened cells extending from the thymic remnants. The small lymphocytes of the thymic remnants played only a passive rôle in the neoplasm.

Scattered about but not numerous were tumor cell clusters, which reproduced more or less the concentric epithelial bodies or corpuscles of the thymus. These clusters were composed of an inner layer of flattened and crescent shaped cells surrounded by more irregular cells. Occasionally, a giant cell formed a part of the inner wall of such structures. In the interior of these bodies, one found desquamated and necrotic cells, and in certain instances, a few intermixed poly-

morphonuclear neutrophilic leukocytes. Keratinization, though not definite, was suggestive in a few of these epithelial bodies. Various transitions of cell clusters to the rudely formed epithelial corpuscles were to be found through the tumor.

The stroma in the more cellular area was rather delicate and composed of fine fibrous tissue. The blood vessels were small, poorly formed and not numerous. However, in large areas the stroma was coarse and gave way to a definite scirrhous type of growth. Intermediate zones of varying degrees of fibrosis were plentiful, but in many places the changes from the cellular to the more scirrhous areas were rather abrupt. The cellular and scirrhous patches were irregularly arranged.

The neoplasm in the fibrosed areas presented the typical structure of a scirrhous carcinoma. The tumor cells had grown in narrow strands or formed large irregular masses. The cells in these portions of the tumor were on the whole larger and more irregular than those found elsewhere. The formation of epithelial bodies, with crescent shape and degenerating inner cells, was also a feature. Giant cells like those described in the foregoing were likewise found. The fibrous tissue was generally pale and compact. The connective tissue cells were small, fusiform and irregular. In places the fibrous tissue was almost acellular and probably slightly hyalinized.

In the dense stroma and also to a slight extent among the more cellular portions of the growth, there were tiny patches as well as scattered small lymphocytes, some of which, especially in the cellular areas, were no doubt of thymic origin. These small lymphocytes gave no evidence of local proliferation and were in marked contrast with the epithelial tumor cells. Plasma cells were fairly numerous in the scirrhous portions of the neoplasm.

The sections from the small deeply placed tumor in the lower pole of the right kidney revealed a characteristic scirrhous type of epithelial tumor. It was almost similar to the scirrhous portion of the growth described in the foregoing. A prominent feature was the concentric epithelial bodies. The carcinoma cells formed numerous small masses, with crescent shaped and flattened inner cells, the latter forming the walls of a tiny central space. These bodies contained desquamated and necrotic carcinoma cells and polymorphonuclear leukocytes, very much like the epithelial bodies found in the primary tumor. Giant cells identical with those in the mediastinal tumor were fairly numerous.

The renal tissue otherwise showed extensive postmortem changes, but the small tumor in the upper pole proved to be a well encapsulated and degenerating hypernephroma. It was undergoing cystic change.

The multilocular cyst of the other kidney was sufficiently well preserved to enable one to feel certain that it also had its origin in a hypernephroma.

Sections from the infiltrated area of the right lung revealed cellular carcinomatous tissue, essentially as already described. Much of this tissue was undergoing degeneration. The hemorrhagic areas of the lungs were apparently hemorrhagic infarcts, probably dependent on thrombosis. Carcinoma cells were not found in these areas. Both lungs were extensively anthracotic. The distended alveoli of both lungs were characteristic of alveolar emphysema. (The slightly invaded hilic tissue of the left lung was not sectioned.)

The lymph nodes from between the primary bronchi were largely replaced by carcinomatous tissue, which was partially cellular, and in places scirrhous in character. The hilic lymph nodes of the lungs presented a similar picture, and all contained much black pigment.

The lymph nodes from the retroperitoneal region showed slight to moderate involvement, with but little or no fibrous tissue reaction.

COMMENT

This case clinically gave evidence of a mediastinal tumor, with interference of the venous circulation of the upper part of the body. The clinical findings at first were interpreted as those of advanced pulmonary tuberculosis, but tubercle bacilli were never found in the sputum. The stereoscopic roentgen-ray examination clearly indicated a large mediastinal tumor, which also involved the right lung.

The cause of death in this case was an acute hemorrhage from the right pulmonary artery into the right primary bronchus. Both of these structures were found to be partially necrotic, as was a large portion of the surrounding tumor tissue.

The gross tumor presented practically the same appearance as do most carcinomas of the thymus. It was a large, adherent and infiltrating growth in the superior anterior mediastinum. The way in which this tumor enveloped and occluded the large intrathoracic vessels, the infiltration of the lungs and the pericardium was characteristic, as was the extension into the neck and the local involvement of the thoracic lymph nodes. The tumor was pyramidal, which was also true in the majority of the reported cases. Gross renal metastasis occurred in the case of Paviot and Gerest, and that of Achard and Paisseau and also in my case. Metastases elsewhere outside the thorax in the various reported cases have involved the liver, the vertebrae, suprarenal glands and retroperitoneal lymph nodes. Invasion of the chest walls anteriorly has also been observed.

Pericardial and pleural effusions, both present in this case, have commonly been observed, especially the former, as a result of direct invasion by the neoplasm of the pericardium.

Microscopically, the neoplasm was made up of two contrasting types of growth, very cellular areas and well marked scirrhous portions. The majority of the carcinomas of the thymus have produced much fibrous tissue and have been more or less scirrhous. The two types of growth were about equally divided, but the more cellular portion perhaps predominated. The renal nodule and certain lymph nodes presented scirrhous metastasis, while those of the right lung and other lymph nodes were very cellular. The flat carcinoma cells were unusually irregular in size and shape, and deeply stained with vesicular nuclei. The rather numerous and large giant cells, which showed peculiar degenerations and inclusions, were noteworthy features. The attempt at formation of concentric epithelial bodies often found in many thymic carcinomas was a distinctive character. This feature was especially well developed in the renal metastasis. The tumor in all probability arose from the reticulum of the thymus, since in places the carcinomatous changes of this tissue in the remnants of the thymus were unmistakable.

The carcinoma cells of the various reported cases have been described, for the most part, as flat cells of various sizes and shapes with vesicular nuclei. Large giant cells, especially mononuclear giant cells, have been described in the majority of cases. In the cases of Achard and Paisseau, Symmers and Vance, Thiroloix and Debré, Sotgia, and Strauss, various attempts were observed at the formation of concentric epithelial bodies, either in the primary tumors or in the metastases or in both. However, some of their interpretations are not so convincing. In certain of these cases there was slight cornification of the epithelium. In Jacobson's case the carcinoma arose from the cells of the concentric corpuscles of the thymus. The presence of few or many small lymphocytes has been a feature in several cases. This was especially true in the case of Kneringer and Priesel, if this case is to be considered as carcinomatous. Remnants of thymic tissue have been found in thymic carcinoma by only a few observers, and Cayley was the first to observe it.

Carcinomas of the thymus appear to have arisen for the most part from the reticular epithelium, and this was true of my case. The carcinoma described by Jacobson sprang from the concentric epithelial bodies.

The involvement of the large veins of the thorax which has occurred in eight of the reported carcinomas of the thymus, including my case, has not been emphasized previously. In both carcinoma cases of Letulle (his seventh and eighth cases) and the cases of Cayley, Achard and Paisseau, Simmonds, Strauss and apparently in Eisenstädt's case, the superior vena cava or tributaries, and in some cases both, had been partially or completely occluded. In certain cases the vessels were thrombosed, in others they were compressed from without, but actual invasion and occlusion by the tumor is not clearly stated by any author. In my case the tumor actually filled the lumen of the superior vena cava and closed off the orifice of the azygos vein, while both innominate, both jugular, and the right subclavian veins were thrombosed. Eisenstädt does not mention the gross appearance of the superior vena cava, but the symptomatology of the interference with the return circulation of the upper half of the body was characteristic. Invasion of the heart occurred in the case of Strauss, the only one of its kind. In Cayley's case the left innominate and its two tributaries were involved, while the vena cava was not narrowed. The azygos vein was involved in the second carcinomatous case of Letulle.

Unfortunately, in not a single instance in any of the seven cases of carcinoma of the thymus, with complete or partial occlusion of the superior vena cava or tributaries, has the collateral venous circulation been worked out. My case is no exception, and in this sense, it is

incomplete. At necropsy, which was performed forty-two hours after death, the dilated veins described by the clinicians were found only in the neck, and at that time they were not especially well marked, and for certain other reasons no attempt was made to dissect the superficial veins.

As is generally known, when the superior vena cava or the innominate veins are partially or completely thrown out of function, the azygos venous system, together with the superficial epigastric veins, returns the blood to the heart by way of the superior and inferior vena cava. Osler,[30] in 1903, presented well such collateral circulation, which developed following occlusion of the superior vena cava and the innominate veins.

In my case, it is easy enough to understand how the blood from the upper extremities returned to the heart, apparently by way of the lateral thoracic veins and the superficial epigastric veins. The superficial thoracic and abdominal veins were noticeably dilated during life. The blood return from the head and neck, in view of the marked thrombosis of the jugular veins, is difficult to explain, but there is the theoretical possibility of the drainage of these parts by way of the vertebral veins.

The symptomatology and physical findings of thymic carcinoma in general were those of a new growth in the superior anterior mediastinum, often involving the superior vena cava and tributaries. Other mediastinal neoplasms may, however, give a somewhat similar clinical picture. Retrosternal dulness and flatness, so important in the diagnosis of mediastinal tumors, have been recorded in only a few of the reported cases, and unfortunately were not mentioned in my case. The roentgen ray was a valuable means of diagnosis, especially in the cases of Jacobson and in my case. In a few cases the patient originally consulted his physician because of the effects of the secondary growths. The youngest patient was 23 years of age, whose case was reported by Letulle, but the majority were more than 40 years of age.

No doubt a fair number of the upper anterior mediastinal new growths, as pointed out by Letulle, are thymic tumors. In all probability a certain number of true carcinomas of the thymus are disposed of as thymomas, and the disease is probably more common than the reports indicate. The clinical diagnosis of mediastinal "sarcoma" so frequently applied to malignant intrathoracic neoplasms, cannot be justified. Descriptive terminology would be far better for clinical purposes, unless available tissue has been examined microscopically.

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30. Osler, W.: On Obstruction of the Superior Vena Cava, Bull. Johns Hopkins Hosp. **14**:169, 1903.

SUMMARY

Carcinoma of the thymus, in about half of the reported cases, has compressed or occluded, completely or partially, the large veins of the mediastinum, especially the superior vena cava.

I have presented a case of carcinoma of the thymus, occluding the superior vena cava and tributaries, and composed of two contrasting types of growth.

NOTE.—Foot [31] has recently described an interesting carcinoma of the thymus, in a man, aged 45. The man died of a massive hemorrhage into the bronchus, almost similar to my case, and the second of its kind. Clinically, there were symptoms and signs of a mediastinal growth, which had extended behind the right clavicle and had also produced obstruction of the superior vena cava. Postmortem, a large infiltrating and enveloping mediastinal tumor was found which had metastasized to the lungs and had invaded and completely occluded the superior vena cava. The primary tumor presented features of a scirrhous carcinoma, but it was mostly necrotic. Collateral circulation of the upper part of the body is not mentioned. Among other important findings the formation of epithelial bodies with keratinization are described and beautifully illustrated. This is the nineteenth reported case of carcinoma of the thymus, and one of the several presenting secondary changes in the superior vena cava.

31. Foot, N. C.: Concerning Malignant Thymoma, with Report on a Case of Primary Carcinoma of the Thymus, Am. J. Path. **2**:33, 1926.

PLATE 1

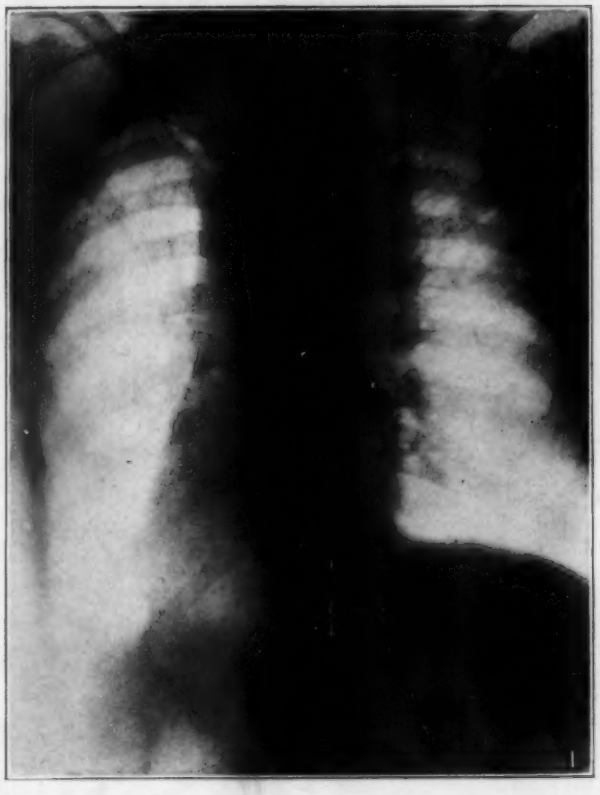

Fig. 1.—Roentgenogram of the thorax showing the mediastinal tumor invading the right lung.

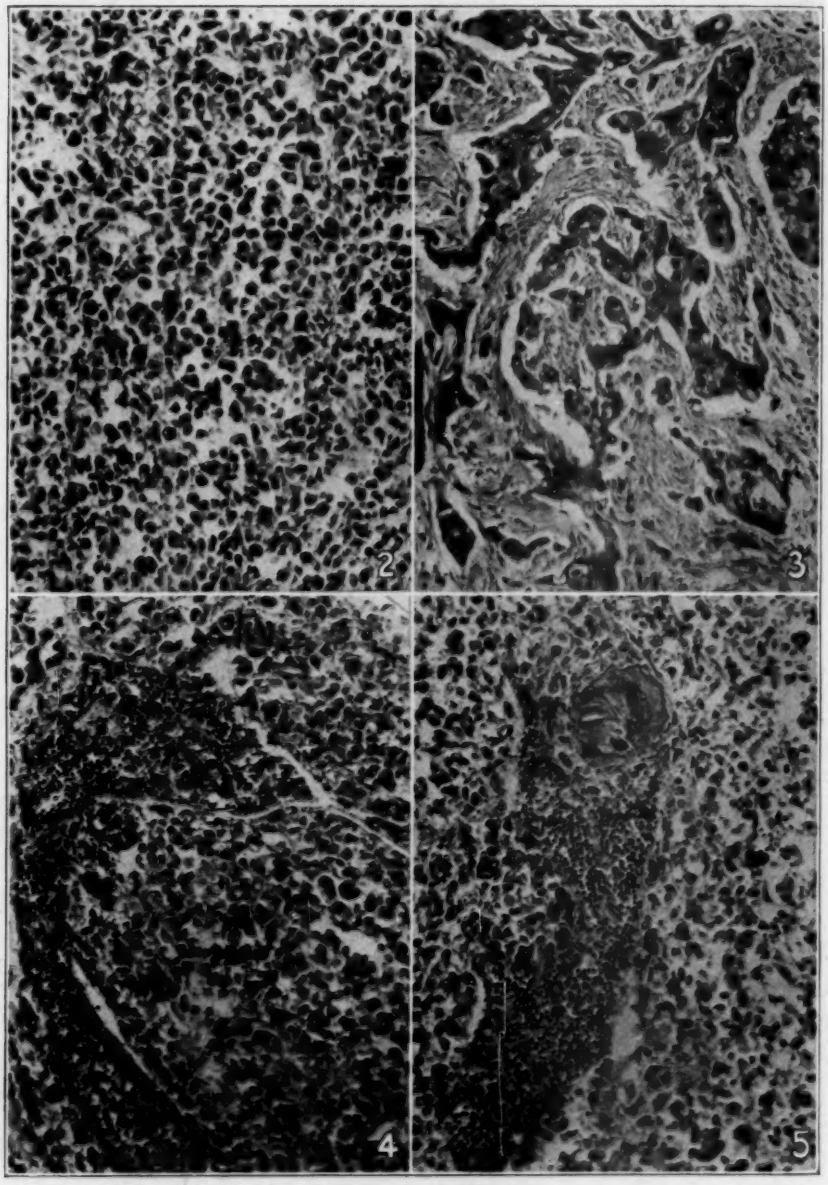

Fig. 2.—Cellular portion of growth.

Fig. 3.—An area of the scirrhous type of the thymic neoplasm.

Figs. 4 and 5.—Relation of the remaining islets of the thymus with the neoplasm. A dilated or cystic concentric epithelial body is shown in figure 5.

PLATE 3

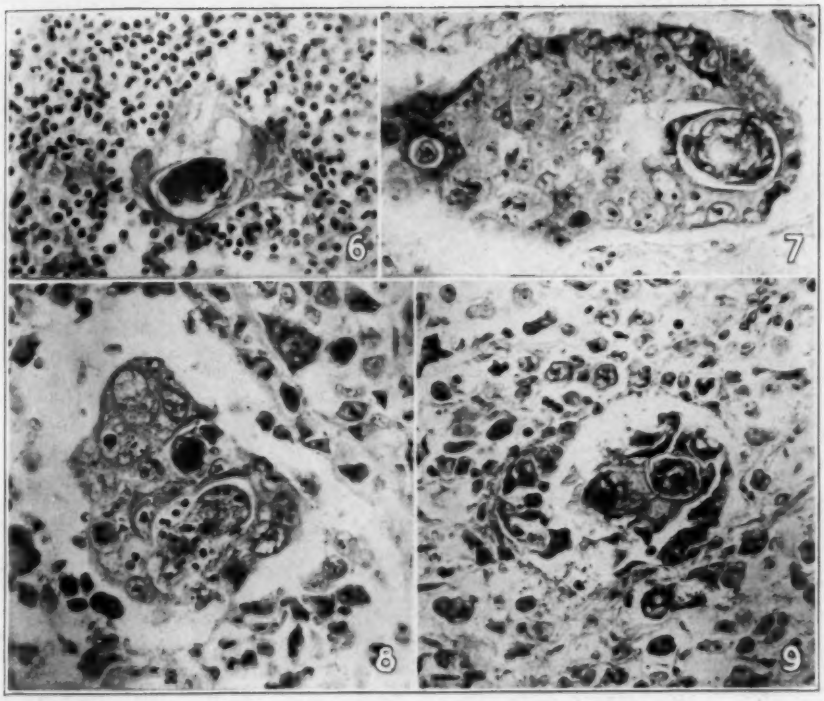

Fig. 6.—A normal concentric epithelial body found in the edge of the thymic tumor.

Figs. 7, 8 and 9.—Various attempts at the production of concentric epithelial bodies found throughout the tumor. A few polymorphonuclear leukocytes are seen in the epithelial body in figure 8.

Laboratory and Technical Notes

MANGANESE IN URINE

Its Detection and Determination *

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Most investigators who have analyzed animal tissues and products for manganese agree that none or very little is to be found in urine. Its presence in small amounts in many common plant foods, and in some animal foods, such as liver, has been shown. Research has shown further that it is found in the blood in small amounts and that it may be found at times in practically all the tissues of the animal body. Whether it enters the body by absorption from the digestive tract, by inhalation as dust, or by intravenous injection, it is said to be eliminated in the bile and feces. After condensing a liter of urine to small volume, in one of his experimental studies, Harnack[1] found manganese by means of the spectroscope. He concluded that manganese absorbed from the digestive tract was for the most part eliminated in the feces, but in very small amounts by the kidneys also. Piccinini[2] makes a similar statement.

We were called on recently to examine the urine of five patients from a manganese grinding plant. The cases have been reported in full by Gayle.[3] Preparatory to making the tests the specimens of urine were treated much the same way as in an analysis for lead or mercury. A large volume of the urine in each case was mixed with concentrated nitric acid in the proportion of 5:1, and the mixture evaporated to a paste in a dish. The residue was then thoroughly digested in a Kjeldahl flask with concentrated sulphuric acid and more nitric acid until oxidation would go no further. After cooling, the residue was acidified with nitric acid, and diluted to about 50 cc., and bismuth dioxide (sodium bismuthate) was sprinkled into the solution. In three cases permanganic acid was shown by the development of the characteristic pink color. The colors tended to disappear in a few hours, but they returned on the addition

* From the Bio-Chemical Laboratory of the Medical College of Virginia.

1. Harnack, E.: Ueber die Resorption des Mangans, Arch. f. Exper. Path. u. Pharmakol. **46**:372, 1901.

2. Piccinini, G. M.: The Resorption of Manganese and the Law of Minimums Between Manganese and Iron, Arch. di farmacol. sper. **10**:419-436, 1910; Chem. Zentralbl. **1**:823, 1911.

3. Gayle, R. Finley, Jr.: Manganese Poisoning and Its Effect on the Central Nervous System. A Report of Six Cases, J. A. M. A. **85**:2008-2011, 1925.

of more of the dioxide. By comparing the unknowns colorimetrically with known amounts of potassium permanganate it was ascertained that one sample contained about 5 mg. of manganese per liter (5 parts per million), and the other smaller amounts. We found it possible to recognize the pink color of permanganic acid in acidified potassium permanganate solutions containing 0.1 mg. of manganese in about 500 cc. of distilled water. By condensing a liter of normal urine by the foregoing procedure, then diluting to 100 cc. and testing and finding a perfectly colorless solution, we reached the conclusion that any manganese in normal urine must be less than 1 part in about 50,000,000.

The most serious objections to the foregoing procedure are that the phosphoric acid liberated during the digestion attacks the glassware, and that the resulting silica and the insoluble bismuth sulphate that slowly precipitates out after the addition of the bismuth dioxide interfere with an accurate and prompt comparison of colors. Both of these substances settle by gravity, and both are removed by centrifuging, but their presence is very objectionable. About forty experiments were made on specimens of normal urine containing added amounts of manganese sulphate, and on some solid animal and plant tissues, to find a better method of procedure. All the principles applied have long been well known, and the procedure we outline below as the best we found has been used in whole or in part in manganese work by previous investigators, such as Harnack, Piccinini, Bertrand,[4] and Reiman and Minot,[5] but none of these seem to have paid much attention to urinary analyses.

ANALYTIC PROCEDURE FOR MANGANESE IN URINE

To 100 cc. of urine in a Kjeldahl flask, 20 cc. of concentrated nitric acid is added. If the urine contains less than 1 mg. of manganese per liter of urine, larger amounts in the same proportion are used. This is followed by evaporation to a paste on a sand bath; after cooling, 5 cc. of concentrated sulphuric acid is added. The preparation is then heated at high temperature until about a third of the acid is driven off as heavy white fumes. With urine high in phosphates, or when a large quantity of urine is used for the analysis, the amount of sulphuric acid may have to be increased. After cooling, 5 cc. of concentrated nitric acid is added, followed by heating until brown fumes disappear. If oxidation does not seem to be complete, this step is repeated again and again until there is no doubt, more sulphuric acid being added if

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4. Bertrand, G., and Medigreceanu, F.: Recherches sur le manganese normal du sang, Ann. de l'Inst. Pasteur **26**:1013, 1912; Recherches sur la presence et la repartition dans les organes des animaux, ibid. **27**:1, 1913. Bertrand, G., and Rosenblatt, M.: Manganese in the Vegetable Kingdom, Ann. de l'Inst. Pasteur **35**:815-819, 1921; General Presence of Manganese in the Vegetable Kingdom, Compt. rend. Acad. de méd. **173**:333-336, 1921.

5. Reiman, C. K., and Minot, A. S.: A Method for Manganese Quantitation in Biological Material Together with Data on Manganese Content of Human Blood and Tissues, J. Biol. Chem. **42**:329-345, 1920. Hamilton, Alice: Industrial Poisons in the United States, New York, The Macmillan Company, 1925, pp. 291-296.

necessary. After cooling, transfer is made to a 100 cc. volumetric flask by means of about 75 cc. of distilled water. Then 5 cc. of concentrated nitric acid, 1 cc. of tenth normal silver nitrate and 1 cc. of 50 per cent ammonium persulphate are added and diluted to the mark. One or more standards are prepared with similar amounts of reagents from manganous sulphate or manganous nitrate, or potassium permanganate in 100 cc. flasks, and both the known and the unknown are heated at the same time in the water bath until the formation of permanganic acid is complete. If the depth of color in the unknown is deep enough comparison is made in the colorimeter, or in Nessler tubes if it is too faint. When manganese is found a blank test should be made on the reagents as a control.

In case the acidity is already quite high due to using more than the amount of sulphuric acid recommended, less nitric acid may be used before adding the persulphate, or its use may be omitted. In case much silica from the glassware is present, it may be ignored until after the solution is made up to volume and the color developed. Then it may be removed from a portion by centrifuging, or it may be allowed to settle by gravity.

The last four experiments of our series of about forty were determinations on unknowns prepared by one of us and analyzed by the other according to the foregoing procedure. The results are given in the table.

While it would seem possible to find one part of manganese in several billions of distilled water by condensing a large volume to a small one before

Results of Experiments by Indicated Procedure

Urine Used for Analysis Cc.	Manganese Present Mg. per Liter	Manganese Found Mg. per Liter
100	2.04	2.18
100	0.96	0.93
100	2.00	2.08
200	0.22	0.21

applying the test, there is a limit to this procedure with urine because of the difficulty in getting rid of the phosphates. We found it difficult to make use of more than 2 liters in any analyses, and found it desirable to work with smaller quantities. It is obvious that reducing substances coming in contact with the permanganic acid will decolorize it and cause negative or low results. The metallic parts of the colorimeter cups must not be overlooked in this connection. On the other hand, the test is so sensitive that the clinician cannot be too careful about protecting the specimen of urine from contamination. The dust from the air of a manganese grinding plant or that from a worker's clothes might easily cause analyses on specimens of normal urine to be positive, or those on pathologic specimens to run much higher than they should. Urine contaminated by feces, in animal experimentation work, may cause wrong conclusions.

SUMMARY

Three cases of manganuria have been added to the very few previously recorded in medical literature.

A colorimetric method has been outlined for the qualitative detection and the quantitative estimation of manganese in urine.

The amount of manganese in one normal urine has been found to be less than 1 part in 50,000,000.

A BLOOD PIPET CARRIER*

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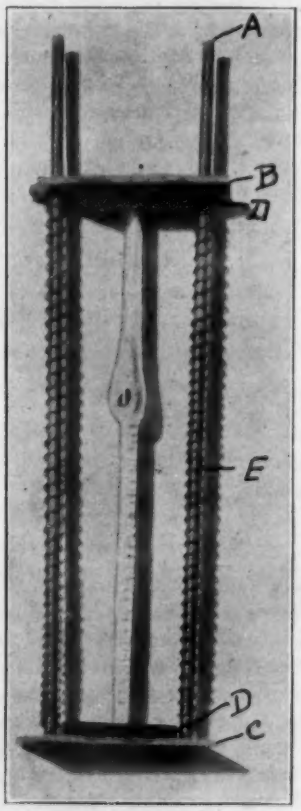
The device pictured in the accompanying illustration has served as an accident proof blood pipet carrier for a considerable period. It consists of two brass rods (*A*) which measure one sixteenth by five and three quarter inches (0.1 by 12.8 cm.). At one end of these rods there is affixed an aluminum plate (*C*) which measures three-fourths by one-sixteenth by one-half inch.



The rods are passed through holes in this plate and riveted. At the other end is a similar plate (*B*) which slides on the rods. The opposing surfaces of the plates have cemented on them pads of rubber (*D*), part of an old door mat being used. The rods are covered by a spring (*E*), the ends of which are passed through the holes in the plate and fastened. The spring is of such a tension that when not extended it measures three and a half inches (7.7 cm.) but it can be extended the full length of the rods.

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* From the Achelis Laboratory, Lenox Hill Hospital.

The pipet after being filled is placed either point down, or up, on one of the pads; the apparatus is then extended, and the other end of the pipet is slipped into place. The pressure of the spring is sufficient to close both ends tightly, preventing leaking. The rubber pads cannot be perforated by the tip, and the side bars prevent the pipet from slipping out of position. Pipets from three and seven-eighths to five and one-half inches can be accommodated without adjustment. If pipets of the same length be selected and the plates widened, two or more pipets can be carried in the same apparatus.

General Review

LOCAL OR TISSUE IMMUNITY*

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If conditions of local immunity are as definite and frequent as recent investigations appear to indicate, we have not only new possibilities of prevention and therapy, but what is really more important, a new method of approach to the understanding of immunity in general. Few, I believe, would question today the generality that body cells, rather than body fluids, are the first and the last factors in the defense processes against micro-organisms. Although body fluids may have marked antibacterial properties which may be enormously increased by immunization, these properties, the so-called antibodies, unquestionably originate in cells. And again, cells are directly responsible for protection through phagocytosis.

A strictly localized form of immunity eliminates humoral factors, which are in their nature universal, and facilitates further analysis by restricting the number and types of cells involved.

We assembled in review form some two years ago the rapidly accumulating evidence on which a conception of local immunity is based. The continually accelerating flow of publication on this subject renders it desirable to attempt another survey in the interests of clearer definition.

SKIN IMMUNITY

Anthrax Immunity.—In spite of the fact that anthrax was the first disease of proved bacterial causation and the second bacterial disease in which a successful method of prevention was obtained (Pasteur), much remains obscure as to the precise method of infection and immunity in various animals. The recent discussion of local immunization has provoked a flood of enlightening communications in respect to this particular infection.

Pasteur's method of subcutaneous inoculation in sheep and beef cattle with two vaccines of successively more virulent anthrax bacilli, has proved most efficient in preventing both natural and artificial anthrax infection. Infection is recognized to take place usually in these animals through the ingestion of spores in contaminated fodder, and led Koch

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to assume in the early history of anthrax immunization that Pasteur's method, although successful in preventing artificial infection through the skin, would be less effective under natural conditions. But Pasteur's method, while relatively effective in the large herbivorous animals, is difficult to employ in protecting the smaller laboratory rodents (rabbits and guinea-pigs), who are extremely sensitive to experimental infection. An analysis of the latter condition was in part responsible for leading Besredka to elaborate his ingenious theory of the importance of local immunization of the portal of entry.

Besredka (*a, b, c, d*) has restated the generally accepted dogma that irrespective of the final distribution of an invading micro-organism, some particularly vulnerable portal of entry is essential for infection: the intestinal tract in typhoid, dysentery and cholera; the skin in anthrax, variola, streptococcus and staphylococcus infections. He has further asserted that protection against any one of these infectious agents is entirely dependent on the local immunization of the specific portal of entry irrespective of any generalized reaction of other cells in the body as evidenced by the coincident presence of antibodies in the serum.

To particularize in respect to anthrax: Although spores are responsible for the infection of cattle through the intestine, it appears that considerable numbers of them are necessary (Sobernheim). In guinea-pigs and rabbits asporogenous bacilli are destroyed by the gastric juice (Sanarelli, *b*), but spores readily invade the blood either from the intestinal canal or the lung and may remain phagocyted within cells for a number of days without harming the host. If the resistance is lowered by increased temperature, the local injection of lactic acid or the intravenous injection of water, septicemia and death rapidly follow. When such blood-containing spores are withdrawn through the skin (Bonquet), a fatal infection from this source may follow. This is confirmed by the work of Basset on the pathogenicity of spores injected into the injured as against the uninjured subcutis.

When vegetative cultures of anthrax rather than spores are injected into small rodents, they frequently fail to kill provided (Besredka) the skin is not infected by the hypodermic needle in its passage into deeper structures. If, however, the skin is contaminated by even the smallest amount of culture, the animal dies. This has led Besredka to assume that the skin is the most or the sole vulnerable organ for this particular micro-organism; he further asserts that protection of the skin and consequently of the body as a whole can be obtained by skin immunization only, and is independent of the presence of antibodies. Immunization by other routes failed completely in his hands.

This concept of Besredka which forms one of the essential arguments in favor of his "portal of entry immunization" theory is based on mis-

conceptions. In the first place, he has overlooked the well-known property of the anthrax bacillus to adapt itself to bodily conditions, provided it be protected from the antagonistic properties of the blood long enough. This it is able to do with certain avirulent cultures and in certain doses, provided the culture is deposited intradermally or on the skin surface as in his experiments. That this is the mechanism of the superior infectivity of Besredka's cultures intradermally has been shown conclusively by Combiesco and Dumitresco. Combiesco repeats an observation that had long been known (Sobernheim), that under normal conditions outside the body the anthrax bacillus is nonencapsulated. It readily assumes this capsule if protected from phagocytosis in the animal body, or will form it in the test tube if whole blood or inactivated serum is added to the culture. When such encapsulated or virulent cultures are injected directly into the blood stream, they are not subject to phagocytosis or the anthracidal effect of body fluids, and under these conditions a fatal result follows (Gratia).

The failure of Besredka to immunize by routes other than the skin is due likewise to the use of a nonencapsulated culture which is deprived of certain of its antigenic properties, as Supniewski has succeeded in immunizing by intraperitoneal injections of phenol-killed encapsulated organisms. When nonencapsulated bacilli were employed intraperitoneally, no immunity resulted; nor did immunity occur in the skin when leukocytes had been artificially attracted there and encapsulation thereby prevented.

The presence or absence of antibodies to anthrax in skin immunization (Besredka) is a matter of no especial significance. Gratia indeed found antagonistic substances present in the serum of skin immunized animals in the sense that simultaneous injection of such serum with the culture protected against skin infection. Apparently the local concentration of the protective substances is essential to protect against skin infection in rabbits even when a commercial anti-anthrax serum is employed (Jonescu-Mihaesti and Combiesco).

There is no doubt that anthrax infections are virulent intradermally and probably in other animals like the calf (Vallée) and rat (Hababon); the reason has already been given.

There is now also evidence that any area with relatively slight blood supply, such as the testicle (Sani), brain (Adelheim and Katkin, Cernainu) or muscle (Basset, *b*), is at least as susceptible as the skin.

In other words, skin susceptibility to anthrax infection is not specific, but due to a relative absence and slow mobilization of protective cells and fluids in that area which allows cultures of sufficient virulence to adapt themselves (capsule or aggressin formation?) and become invasive. Skin immunization is due in a similar manner to reconstruction of

certain necessary antigenic properties of the anthrax bacillus, and the relatively prolonged residence of the bacteria before destruction (Wollman).

Anthrax infection, then, is not a very useful illustration of local immunity and the possibilities of local immunization; nor is anthrax primarily a skin infection in the sense that the skin is the only susceptible tissue.

This disagreement with Besredka's point of view in respect to anthrax in no way minimizes the possible usefulness of skin immunization as a most efficient method of preventive vaccination of various animals against this disease. Recent publications by Velu and Vaysse, Velu (*a, b*), Nicholas, Velu and Bigot all point to the applicability of skin vaccination, but such promising results should not influence us in favor of Besredka's interpretation of them.

Vaccine Immunity.—In one of his earlier reviews, Besredka (*b*) referred to some unpublished experiments which indicated to him that his theory of localized immunization was fully supported by the essential facts of vaccine immunity. Since no specific publication of his work on this problem has to our knowledge appeared, and since his later reviews (Besredka, *d*) contain no reference to this question, we are justified in considering his assertions in the light of information that has long since been available. Tomarkin and Carriere in 1913 considered the subject of vaccine immunity, and so far as we are aware no subsequent facts have been presented which would refute their main conclusions.

There is general agreement that vaccine is a dermotropic virus, and almost general agreement that vaccine immunity is histogenous rather than due to the presence of antibodies. The work of Calmette and Guerin showed clearly that rabbits can be immunized irrespective of the route by which vaccine is administered, whether subcutaneously, intratracheally, intrapleurally or intravenously. In none of these instances are pustules formed, and at the end of twenty-four hours no organ or fluid contains the virus. If the skin, however, is abraded at this period, but not later, a characteristic eruption appears there, showing that an intradermal localization is rapid and complete. Injection into the brain substance preserves the virus for as long as four days. These results, which have been confirmed by others, overwhelm Besredka's assertion that the intradermal route of immunization is essential. No pustule formation is necessary to insure protection (Kraus and Volk), although it serves a useful purpose in practical immunization. Vaccination is also possible by a heat-killed virus.

There seems little doubt that the earlier stages of immunity against vaccinia are accompanied by antagonistic properties (viruscidal properties) in the blood serum (Camus), but these disappear long before

protection is lost. Besredka has admitted these facts, but urges that they should not be interpreted as indicating the humoral nature (Sato) of vaccinia, with which point I agree. There is no evidence that continued protection of the epidermal cells is due to a storing up of antibodies, but rather to some allergic predisposition.

An early suggestion of Pfeiffer's that vaccine immunity might conceivably be due to continued residence of the virus in the specific cells was found by him to have no experimental support.

Corneal immunity in the rabbit against vaccine virus affords the most convincing evidence that the immunity is confined not only to the epidermal or dermal cells, but also that it may be restricted to a small group of them. Kraus and Volk have shown that inoculation of one cornea in the rabbit leads to its protection, but not to the protection of the other cornea. Skin vaccination, on the other hand, will not protect the cornea. Although these conditions may not be inviolable and although it may be true that skin immunity may follow corneal immunity slowly, or that subcutaneous injection of vaccine in sufficient doses will protect the cornea, the fact that a strictly localized area may be protected before the rest of the body seems to be well established. As illustrative of the opposing conception that vaccine immunity is general rather than confined to the epithelium, the statements of Othwara should be mentioned.

We have, then, in vaccinia-variola infections, an instance of an organ or cells with peculiar and sole susceptibility to a virus; and the protection of these cells depends on the localization of the virus in them for a time. An individual group of the cells may actually be exclusively protected as in the cornea. Apparently localization in the epidermis occurs irrespective of the route of introduction of the virus. We are dealing with a true instance of local immunity.

Streptococcus and Staphylococcus Infections.—Streptococcus infections when localized or beginning in the skin, as in spontaneous and experimental erysipelas, have been considered from the standpoint of local immunity ever since the pioneer work of Fehleisen. We have several times reviewed the literature on this subject (Gay and Rhodes; Gay and Morrison; Gay, *a, b*), and may here confine ourselves to a restatement of our previous conclusions.

Under proper conditions of dosage and intervals it may be shown that streptococcus infections give protection in the area of skin employed, for example one ear, as compared with other similar superficial areas in the body (Cobbett and Melsome); or under other conditions, skin inoculation is followed by relative resistance of the skin of the whole body as against other routes of infection (Gay and Rhodes). Such observations led Gay and Morrison to point out the relation of such localized protected areas to large mononuclear cells of the "clasmatocyte"

or "histiocyte" type. This relationship is more evident when the local resistance or active or passive immunity of the rabbit pleura is considered (Gay and Morrison; Gay and Clark).

Similar observations contributed to Besredka's (*d*) ideas of the possibilities of local immunization in superficial streptococcus and staphylococcus infections. By the simple application of bandages soaked in the filtrates of a streptococcus or staphylococcus culture to the skin of guinea-pigs, a local protection against the corresponding organism was obtained which was judged to be specific (Besredka, *a, e, f, g;* Besredka and Urbain). This action is supposed to be due to an "antivirus" in the specific filtrate which in some manner protects the receptive cells (Besredka).

We feel convinced that the results which Besredka undoubtedly obtained are due entirely to the stimulating effect of broth on a particular group of cells and is in no wise dependent on any specific substance in the bacterial filtrates. At all events, we had already obtained similar results (Gay and Morrison) by the injection of broth in preventing the much more fatal streptococcus pleurisy of rabbits. Gratia (*b*) obtained precisely the same degree of protection in guinea-pig skin infections with broth as with filtrates or autolysates of bacteria. The latter results have been confirmed and extended by Rivers, by Rivers and Tillett, and by Mallory and Marble.

Surely here the conception of a specific "portal of entry" cannot be invoked with such indiscriminate organisms as the staphylococcus or streptococcus whose localization in the superficial layers of the body depends entirely on inability to push on further, or rather whose check at this point depends on adequate local defense under the particular conditions and time. Protection of the skin against staphylococcus, moreover, may be produced by immunization through the mouth (Combiescu and Calab).

As in the case of intradermal anthrax immunization, a flood of clinical observations has followed Besredka's suggestions on the protection of laboratory animals by culture filtrates of staphylococcus and streptococcus ("antivirus"). These observations, interesting as they are, and practically important as they may prove, afford a group that must ultimately be subjected to quite a different type of analysis from controlled laboratory experiments. These small groups of clinical cases are scattered through the French medical literature of the past few years and have faithfully been assembled by Besredka (*i*) in his latest monographic presentation of his thesis on local immunization. It seems justifiable to state that even in this extensive presentation of his views Besredka steadfastly refuses to discuss or even to mention most of the critical objections to his theories that we have referred to, and the clinical application of his ideas are blindly empiric. For example, in the

present connection, no effort is made to check the mechanism of the alleged therapeutic effect of culture filtrates by the use of plain broth. No attempt is made to investigate the alleged "antivirus" effect which appears in a single day, or to do more than state in the most general terms what the "activation of the defensive mechanism" of the body cells may be (Besredka, *h*).

IMMUNIZATION BY MOUTH

Besredka deserves great credit for bringing forward again the question of immunization by mouth. Although attempts to immunize by this unobjectionable route have long been tried (Calmette), Besredka has given the idea prominence, and indeed a certain promise, in the light of the practical results which his followers seem to have obtained. But we repeat with Ledingham (discussion to Besredka, *j*) that "field experiments are in a different category from experimental data and must be differently assessed." The infections that have recently been considered most are the typhoids, cholera, dysentery and tuberculosis, all of which concern the intestinal canal, either as a portal of entry (tuberculosis, typhoid) or as a localized site of infection (cholera, dysentery). We are not certain how two such divergently extending infections as dysentery and typhoid should properly be interpreted in Besredka's sense.

I am confining the discussion again entirely to the experimental results in animals, and in the previous review noted the rather general failure to repeat some of Besredka's experiments. Most agreed that the administration of bile to rabbits lowered their resistance to cholera and typhoid, but several (Zingher and Soletsky, Neri) failed to obtain successful immunizing results. To this list must now be added the names of Teale and of Gye (Besredka, *j*). In fact, we find no further confirmation of the typhoid immunization in animals.

In the case of dysentery (Shiga) no bile is needed; rabbits can undoubtedly be killed with a characteristic lesion of the cecum, and that irrespective of the route employed. It seems, moreover, that immunity can definitely be produced by mouth (Magheru and Calab, Enlows). But protection and apparently just as good protection, or better, can be effected by injection through the skin (Baltiano) or subcutaneously (Enlows, Ciuca and Balteanu).

The same is true with cholera, in which protection may be produced by the mouth. Peverelli and Besredka (*j*) himself, as well as Ciuca and Balteanu (*b*), have shown that filtrates of cholera vibrios will protect against a fatal intravenous dose, whether given intravenously, subcutaneously or intradermally. This, of course, is compatible with the idea that the intestinal mucosa is the susceptible area but is not identical with its consideration as a portal of entry.

Again we have such observations as those of Combiescu (*b*) which show that skin infections with staphylococcus can be prevented by vaccination by the mouth.

IMMUNIZATION BY THE RESPIRATORY TRACT

I have previously discussed the possibilities of protecting animals, both locally and generally by injecting bacteria through the lungs. They seemed significant so far as pneumococcus is concerned (Cecil and Steffens), but less obvious in the numerous experiments with the typhoid bacillus (Besredka). Turro and Domingo thought this protection was local, since antibodies appeared in the lung tissue earlier than elsewhere. At all events, no question of the specifically susceptible cells can be raised in these last experiments.

TRENDS IN THE STUDY OF LOCAL IMMUNITY

This brief attempt to depict the present state of our knowledge, largely in the light of Besredka's hypothesis, is purposely offered first for the purpose of demonstrating how far from final this explanation is. The main object of an hypothesis is accomplished, however, if it stimulates further work and other hypotheses.

We believe, in the first place, that there is now overwhelming evidence of the existence of a truly localized form of immunity—an immunity confined under properly chosen conditions to certain tissues, such as the skin or the connective tissue, and probably also confined under certain conditions to localized areas, such as the cornea, or to a small area of the skin, and conceivably in last analysis to a single cell. These localized states of immunity spread imperceptibly from the more restricted to the larger areas, and may then become what we have designated as a general immunity. In the latter condition antibodies are frequently present, although not a direct measure of active protection. Antibodies are usually not present in the various forms of local immunity. Conversely, local immunity in the sense we have used it, is strictly cellular in nature.

My conception of the change which takes place in cells in the acquisition of immunity is that they become more resistant to the infectious agent, rather than "desensitized" (Besredka *i*) to its action. I believe further that such cells may not only be changed qualitatively, but also quantitatively increased.

The question naturally arises as to whether the cell groups that may be locally protected against a given agent by contact with it, are confined to those that are specifically attacked or affected by it. Here the evidence is confused, and more instances that will bear investigation are required. Closely related is the question of the relation of the susceptible cell to antibody formation. So far, of the instances I have

discussed, vaccine immunity offers the sole example of protection which may be localized in corneal epithelium or in the skin as a whole, and in which the virus can propagate only in the tissue concerned. Anthrax is not a skin infection intrinsically, nor is immunity confined to that organ. The portal of entry must not be confused with the locus of minoris resistentiae. Although the portal of entry in typhoid is through the intestine, the area of selective action, both in man and rabbits, is the bone marrow and gallbladder (Gay, *c*). It may still be true that closing the portal of entry by immunization will protect, but this is not equivalent to saying that the specifically susceptible cells have been immunized. In other words, throughout the discussion the purposes of "localized immunization" have somewhat obscured the phenomenon of local immunity.

The consideration that is now being given to local immunity will lead to a more purposeful understanding of the general processes of immunity. This, I believe, lies in deeper understanding of the cell changes involved, as stated in the beginning of this article. Stimulating as the knowledge of the humoral aspects of immunity has been, they have not been finally satisfactory intellectually, and again the usefulness of passive serum therapy has been limited to a few examples. Further progress in immunology, both theoretical and practical, must depend on a new "lead," or on better understanding of generally accepted ideas. The idea that it is the cells that are affected ultimately in the pathogenic activities of bacteria, the particular type of cell that is specifically attacked by any given micro-organism, the idea that a certain variety of cells form each particular variety of antibody, and correlatively that such cells are responsible for active immunity, are all vague and undefined notions, scarcely to be tagged in any instance.

It is with this general point of view that we have reiterated in recent years the growing significance of a certain type, or types of cells, in relation at least to certain instances of local immunity.

We believe that the cells which Metchnikoff designated as "macrophages" have never been sufficiently appreciated by him or others as protective agents against extraneous micro-organisms. We now are tending to include rather more varied cell groups under this heading than before. There is no question as to some generic relationship between the monocytes of the blood, the clasmatocytes (histiocytes, tissue macrophages) of the connective tissue, the endothelium, at least of capillaries, and Kupffer's cells of the liver. The histogenic relationship of these cells, their transformation from one into the other type under varying conditions, and such matters, are actively engaging the attention of the ablest histologists, and do not primarily concern us. What interests us as immunologists is, first, a fundamental function of phagocytosis that all of these cells seem to enjoy. Implied therewith is

the recognition of the association of these cells in the varying types of infection and resistance. These cells are very resistant, and the clasmatocytes and monocytes at least are readily motile. All of the cells, moreover, are ubiquitous. All these facts indirectly make them worthy of consideration in conditions of immunity, local and general, and in connection with antibody formation. These facts are not true of any of the fixed tissue cells.

We have referred previously to the observations of Issaef, Durham, Jensen, Noetzel (*a, b*), Wallgren, Beattie, Buxton and Torrey, all of which indicated that "clasmatocytes" (formerly called "endothelial" cells) have an important function in freeing the peritoneal cavity from bacteria. Another series of observations have emphasized the important phagocytic function of vascular endothelium in the disposal of bacteria (Werigo, Adami, Abbott and Nicholson, Kyes, Nagao, and Motohashi, (*a, b*). These facts are now extended by Siegmund, Jungman, Herzog, Permar, Oerskov and Donagh.

The "clasmatocytes" or macrophages of connective tissue have the advantage of a clear definition that can be made on the basis of vital (trypan blue) or supravital (neutral red) staining, whatever decision may ultimately be made as to their relationship to monocytes or endothelium. Cells presumably of this type have long been considered in connection with reparative processes and in relation to increased resistance, particularly in the streptococcus infections (Gay, *b*). Our own work (Gay and Morrison; Gay and Clark) gave the cells a quantitative as well as an exact qualitative significance in experimental streptococcus pleurisy. These observations have been extended to other bacteria by Katsuma and Suma with staphylococcus, and to colon bacillus by Nakahara.

Our observations showed the importance of clasmatocytes not only in increased resistance produced by agents like broth, but also in specific active and passive immunity. Our published studies have shown the various degrees of protection as paralleled by the total number of clasmatocytes in the pleural cavity and also by their preferential phagocytic ability over polymorphonuclear cells, which seem to have little protective function in streptococcus infection. Unpublished observations show that the local destructive action of the exudate itself is probably not the decisive factor involved; although protection is confined to animals with exudates in the mononuclear stage, polymorphonuclear exudates yield bactericidal substances in even greater concentration than clasmatocytes, owing to the larger total number of cells involved. Further, the relatively slow destruction of streptococci by these bactericidal substances does not suffice to explain the rapid disappearance of the bacteria from the pleural cavity in effectively protected animals.

We now find that the histologic background of the pleural exudates is apparently the significant factor in local streptococcus protection. It is found that in the relatively simple tissue of the rabbit pleura changes occur on inducing increased resistance or active immunity to streptococcus that are roughly proportionate to the degree of protection acquired. These changes are simply the formation of granulation tissue. The drainage of the pleural cavity, both for dye and carbon particles as well as bacteria is entirely through the parietal wall and diaphragm, the lymphatics of which drain into the retrosternal nodes (Gay and Rhodes, *b*; Karsner and Swanbeck).

In the increasing grades of protection the subserous layer of the pleura, slightly on the visceral side and much more markedly on the parietal and diaphragmatic surface, increases in thickness from an initial width of about 30 microns to as much as 1,100 microns, or nearly forty times. The subserosa is increased in thickness by the infiltration of enormous numbers of mononuclear cells, which following injections of trypan blue in the cavity can be shown to be, in significant proportion, true clasmatocytes.

Moreover, bacteria injected into the pleural cavity are found in an hour or two in the clasmatocytes of the subserous layer under an apparently intact, though modified, serosa which is never in itself phagocytic.

Such observations form, we believe, the basis for a more exhaustive study of the histology of immunity. They have of course been predictable by such observations as those of Treves, which indicated that previously operated peritoneal cavities offered a better chance of recovery from infections; and those of Katzenstein, who found that skin flaps grafted from previonsly infected areas were more resistant to infection, as well as the more recent evidence of a local type of immunity. Of more direct bearing is the generally accepted surgical aphorism that granulation tissue is difficult to infect (Adami). It has only recently been shown by Gaza that the granulation tissue of open wounds contains significant numbers of true clasmatocytes. It is by no means generally accepted that sterilization in granulating wounds is due entirely to the activity of these or other cells; Bergel, for instance, thinks that fibrin is the responsible element.

The walling off of an abscess by connective tissue is another process of apparently the same nature. It has recently been shown in an interesting way by Opie that a foreign protein remains in an area of the skin that has been immunized against it. In a similar fashion Willis found that virulent tubercle bacilli when injected into the skin of guinea-pigs that have been immunized by intradermal injection of a nonvirulent organism in the same area are delayed for as long as two or three weeks in passing to the adjacent lymph node. It is evident that in both these processes a similar mechanism of cell defense has been erected.

Although there seems to be an actual quantitative relation between the number of cells produced in immunization and the degree of protection acquired, we by no means disregard the qualitative element involved in individual cell change or the adjuvant effect of antibodies. The relationships here involved require much further study and control. But at all events, the cell increases described seem to explain strictly local immunity most satisfactorily. They may even be applicable to a more generalized single tissue immunity as in the resistance of the entire skin in experimental erysipelas (Gay and Rhodes). Here not only is the point of previous infection protected, but any other area of the skin, although not the pleura. Preliminary experiments in pleural immunity indicate that in advanced grades not only is the original pleura protected, but the other pleura as well. In this instance the histology of the pleura opposite the immunized one is normal before infection, but on injecting the test dose protection is acquired by mobilization of previously formed clasmatocytes in the new area.

The difficulty in securing a firm generalized streptococcus immunity has been mentioned. May it not depend on difficulty in reaching or stimulating susceptible or responsible cells? This and other questions of general bearing, particularly as regards the varieties of infection to which this histogenic type of immunity is confined, are matters for the future. The recent work of Cunningham, Sabin and co-workers indicates that tuberculosis at least is another instance of this form of protection in which case monocytes rather than clasmatocytes are involved. Similarly, the histologic studies of Meleney implicate the clasmatocytes in kala-azar. I believe that both these studies, however, have emphasized cell involvement rather than cell protection.

THE LOCUS OF ANTIBODY FORMATION

This review cannot logically be concluded without brief reference to the series of studies that implicate the clasmatocytes in antibody formation.

Several authors, notably Kraus and Schiffmann, and recently Eastwood and Siegmund, have concluded largely on literary and theoretic grounds that the capillary endothelium is the site of antibody formation.

The relation of the reticulo-endothelial system in its larger sense to antibody formation is more directly proved by the method of dye blockade. The particular cells attacked would depend on the substance employed. Trypan blue at least will not accumulate in the endothelium in the characteristic form in which it does in the clasmatocytes. The work of Migay and Petroff, and particularly of Kusnetowsky, has shown us that the absorption of one colloid prevents the subsequent absorption of a different one. The work of Vanucci, of

Standenath and of Rosenthal and Petzel with blockade by dyestuffs and China ink followed by antigens led to opposite and inconclusive results. Gay and Clark (*b*) and more recently Isaacs have shown that hemolysin formation in both rabbits and guinea-pigs can be conclusively inhibited by injections of trypan blue. Paschis has brought out the reverse phenomenon in an interesting way; the phagocytosis of bacteria may prevent subsequent absorption of dye.

Lewis and Loomis found that tuberculous guinea-pigs produce hemolysins more markedly than do normal animals. Such results were exceptional in rabbits in Hektoen and Corper's experience. The obtaining of diametrically opposite results in antibody formation is not inconsistent. Even with the dyestuffs there is evidence to show (Rosenthal and Petzel) that small amounts of dye will stimulate antibody formation whereas large amounts will prevent it; in other words, the result will depend on whether cell stimulation or cell plugging has been effected.

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Notes and News

D'Herelle Receives Leeuwenhoek Medal.—The Leeuwenhoek medal was presented to F. d'Herelle, discoverer of bacteriophage, at a special meeting of the Dutch Royal Academy of Sciences on Sept. 26, 1925.

Keegan Coroner's Physician in Philadelphia.—Dr. Arthur P. Keegan assumed the duties of coroner's physician in Philadelphia, October 1, succeeding Dr. Richard D. Burke.

New Journal.—*Biological Abstracts,* which is supported by the Rockefeller Foundation, will begin its work with the literature of 1926, and the first issue will appear in May or June, 1926. The central office will be in the zoology building of the University of Pennsylvania. The editor-in-chief is J. R. Schramm.

John Simon Guggenheim Memorial Foundation.—The first general awards will be made in the spring of 1926 for the academic year 1926-1927, when from forty to fifty Fellows will be appointed. Shortly after the establishment of the Foundation, however, letters of inquiry were received from a number of persons who for particular reasons deemed it necessary to go abroad to prosecute their studies and researches during the year 1925-1926. These persons were invited to present their credentials; and from this number, fifteen whose plans were most urgent and, in the opinion of the Trustees, most meritorius, have been selected for appointment in advance of the general awards. Among the advance appointees are: Dr. Percival Bailey, associate in surgery, Peter Bent Brigham Hospital, Boston, Massachusetts; instructor in surgery and director of the laboratory of surgical research, Harvard Medical School; appointed for research diseases of the nervous system, principally in the clinic of M. le professeur Claude, at the Asile Sainte-Anne, Paris, France, and the Laboratory of Dejerine, University of Paris, France. Edwin W. Schultz, M.D., Hopkins, 1917, associate professor of bacteriology, Stanford University, Calif.; appointed for a study of the problem of the bacteriophage, principally under Dr. F. d'Herelle, in the Laboratory of the International Sanitary Council, at Alexandria, Egypt.

Dedication of Rawson Laboratories of the University of Chicago.—The new Rawson Laboratories of the University of Chicago (Rush Medical College) were dedicated with appropriate ceremonies, Dec. 18, 1925. The building is five stories high, of steel construction, joined on one side with the Presbyterian Hospital and on the other with the Senn building. The first floor contains the administrative offices and library; the second, third and fourth floors are for classrooms, examining rooms, reception rooms and special laboratories. Surgery occupies the entire fourth floor, and the Norman Bridge Pathologic Laboratory the fifth floor. The Central Free Dispensary, which last year treated more than 100,000 persons, will be in this and the Senn buildings. There is a children's play room for mothers who, in seeking treatment, bring their children, and a play director in charge. There are small treatment rooms throughout the building, two operating rooms on the fourth floor for minor operations, and various small laboratories for medical research for advanced students. The laboratories and the building generally are of the modern type.

Bust of Dr. William H. Welch.—To commemorate his seventy-fifth birthday on April 8, 1925, steps were taken to secure a bust of Dr. Welch by the artist Konenkov. This bust, presented to Johns Hopkins University by a group of friends, was unveiled at the commemoration day exercises of the university on February 22. Dr. Simon Flexner concluded his address on the occasion as follows: "It is the hope of the committee that, in the discretion of the president and board of trustees of the university, this bust may be so exhibited that succeeding generations without end of teachers and students may come to view it. In contemplating its fine features, its strength and its wisdom, they will be reminded of the great teacher and citizen whose long and noble life's work is being devoted unselfishly, generously and kindly, successfully and modestly, to the advancement of knowledge and to the upbuilding of a school of medicine and allied sciences which has become a model for the world; perchance they will be reminded also that in making others strong resides the greatest strength and the most enduring happiness."

The Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation.—This foundation was established in 1923, and during the first year of its existence thirty-two applications for assistance were received from investigators in the United States, Europe and Australia. Eight grants were made. There has been considerable increase in the number of applications this year, the total being fifty-three. Fourteen came from eleven different countries in Europe and Asia, and the remainder from the United States. One grant for a period of three years has been continued, and thirteen new grants have been made. The list of the researches which have been aided follows:

1. L. H. Newburgh, University of Michigan, $1,250 a year for three years for a study of the production of chronic nephritis with high protein diets and amino acids.

2. Edward F. Adolph, zoological laboratory, Johns Hopkins University, $200 for the purchase of equipment to be used in investigations of the process of secretion with special reference to the kidneys.

3. Francis G. Blake and W. O. Winternitz, Yale University School of Medicine, $1,000 for the purchase and care of animals to be used in the study of the experimental production of nephritis with the toxin of scarlet fever.

4. Lion Blum, faculty of medicine of the University of Strasbourg, France, $500 for the purchase of apparatus to be used in a research on the blood in various pathologic conditions.

5. Alan M. Chesney, Johns Hopkins Hospital, $1,000 for the purchase and care of animals and for other expenses of a research on syphilis.

6. Joseph Erlanger and Herbert T. Gasser, school of medicine, Washington University, $1,000 for the purchase of an apparatus designed to record undistorted single action currents in nerve, to be used in the investigation of the physiology of nerve.

7. Ludwig Hofbauer, first medical clinic, Vienna, Austria, $200 for animals and apparatus to be used in researches on the effect of pathologic conditions of the respiratory system on the body as a whole.

8. Edward B. Krumbhaar, Philadelphia General Hospital, $250 for the purchase of animals to be used in an investigation of biologic resistance to experimental malignant tumors.

9. A. Lipschutz, director of The Physiological Institute, University of Dorpat, Esthonia, $1,000 for animals and apparatus necessary in a research on the internal secretions of the sex glands.

10. William deB. MacNider, University of North Carolina, $1,700 a year for two years toward general expenses of a study of experimental chronic nephritis.

11. C. R. Schlayer, Augustahospital, Berlin, $250 for apparatus to be used in studies of the permeability of tissue to the roentgen ray.

12. Frederic Verzar, director of the physiologic laboratories, University of Debrecen, Hungary, $1,000 toward the expenses of investigation on avitaminosis and internal secretions.

13. Joseph C. Aub, Massachusetts General Hospital, $500 for supplies and equipment to be used in a study of the internal secretion of the suprarenal cortex.

14. H. C. Bazett, department of physiology, University of Pennsylvania, $500 for the purchase of a galvanometer to be used in a research on skin and subcutaneous temperatures.

Applications for grants to be held during the year 1926-1927 should be in the hands of the executive committee before May 15, and should be sent to the secretary, Dr. Francis W. Peabody, Boston City Hospital, Boston.

Abstracts from Current Literature

Pathologic Physiology

THE PRESERVATION OF TESTES FOR TRANSPLANTATION IN RABBITS AND DOGS. N. M. SHUSTROV, S. G. KARPOVA and I. V. TIKHOMIROV, J. Path. and Bact. **28**:651, 1925.

Testes of rabbits were transplanted successfully after keeping in cold Ringer-Locke's solution for five days.

ERNEST M. HALL.

IODINE HYPERTHYROIDISM. A. S. JACKSON, Am. J. M. Sc. **170**:271, 1925.

Iodine hyperthyroidism is promoted by the promiscuous distribution of iodine in water and table salt. It develops only in the presence of an adenomatous goiter. The pathologic changes are not characteristic. Grossly, the gland has the typical appearance of an adenomatous goiter containing degenerated, cystic, fibrous and calcareous encapsulated nodules. Colloid may be present in large amounts. Microscopically the acini vary in size, are lined with flat, cuboid cells and are filled with colloid. Fetal acini and occasional small regions of glandular hyperplasia are found.

ARTHUR LOCKE.

THE EFFECT OF SPLEEN EXTRACT AND BONE MARROW ON THE BLOOD PICTURE IN PULMONARY TUBERCULOSIS. R. W. DUNHAM, Am. J. M. Sc. **170**:394, 1925.

Spleen extract and bone marrow definitely increase erythrocyte and hemoglobin production.

ARTHUR LOCKE.

THE PRODUCTION OF ALBUMINURIA BY RENAL VASO-CONSTRICTION IN ANIMALS AND IN MAN. ISAAC STARR, J. Exper. Med. **43**:31, 1925.

Transient albuminuria follows the infusion of small doses of epinephrin into rabbits, if prolonged over several minutes. Agents causing renal vasoconstriction also cause transient albuminuria in anesthetized, eviscerated dogs. Cats eliminate albumin after having been frightened or enraged.

The drug ephedrine, which commonly causes renal vasoconstriction in animals, has been tested in man. Transient albuminuria followed its administration in those cases in which signs of renal vasoconstriction appeared; it did not in those cases in which such signs were lacking. Evidence was obtained that ephedrine is not intrinsically injurious to the kidney.

The observed facts may be explained by the conception that renal vasoconstriction causes increase in the duration and extent of the normal intermittent interruptions in the glomerular circulation. Permeability of the glomerular membranes is so increased by these lenghtened interruptions that when blood flow is reestablished, albumin escapes.

It is believed that this conception may apply to those albuminurias in man which result from excessive muscular exercise or emotion or which are produced reflexly. It may explain the occurrence of albumin in the urine of normal people and in healthy laboratory animals; it may play a part in the explanation of the albuminuria which occurs after anesthesia or in cardiac decompensation. Its possible relation to orthostatic albuminuria has been discussed.

AUTHOR'S SUMMARY.

SOME UNRECOGNIZED DANGERS IN THE USE AND HANDLING OF RADIOACTIVE SUBSTANCES. HARRISON S. MARTLAND, PHILIP CONLON and JOSEPH P. KNEF, J. A. M. A. **85**:1769, 1925.

An unrecognized occupational poisoning is described, characterized by anemia due to deposition of radioactive elements that act on the centers for blood production, and by necrosis of the jaw from the action of radioactive particles clinging to the gums, teeth and roof of the mouth. By means of electrometers radioactivity has been demonstrated in the body of exposed persons during life as well as after death. The indications are that the presence in the body of radioactive elements may be demonstrable long before any clinical symptoms appear. Once deposited radioactive elements cannot be eliminated, and anemia and possibly other morbid processes may develop without the real cause being suspected. For this reason the intravenous injections or internal administration of long lived radioactive substances may be dangerous. It would seem to be advisable to test the expiratory air for radioactivity in workers in radioactive substances who have anemia and other suspicious conditions.

THE CLINICAL DIFFERENTIATION OF SPONTANEOUS INTRACEREBRAL HEMORRHAGE AND UREMIA. E. R. LECOUNT and C. C. GUY, J. A. M. A. **85**:2003, 1925.

No patient in this series of thirty deaths from intracerebral hemorrhage dying with the clinical diagnosis of uremia had a nitrogen retention comparable to that of true uremia.

In spontaneous intracerebral hemorrhage, the increase of the various nitrogenous elements of the blood above the normal varied from 16 to 43, the creatinin (16 per cent) being the least increased, and the uric acid (43 per cent) the most.

In 67 per cent of the thirty, the gross changes in the kidneys indicated some chronic disease; in 7 per cent, no gross changes of any kind were found.

The presence of blood in the spinal fluid and the great increase in the nitrogenous elements in the blood are apparently the two most important factors in the differential diagnosis between uremia and spontaneous intracerebral hemorrhage.

AUTHORS' SUMMARY.

THE RATE OF ELIMINATION OF INGESTED SUGARS IN PHLORHIZIN DIABETES. H. J. DEUEL, JR., and W. H. CHAMBERS, J. Biol. Chem. **65**:7, 1925.

The rate of sugar elimination by fasting, phlorhizinized dogs after the ingestion of 16 Gm. of glucose, fructose or galactose is practically identical. Lactose is excreted more slowly, and less than 50 per cent of the glucose arising from it is recovered at the end of twelve hours. Fructose is completely converted into glucose, and the converted sugar is almost completely eliminated within five hours. More than 88 per cent of ingested galactose is excreted as glucose. Nitrogen metabolism decreases following carbohydrate ingestion although the sugars are not absorbed and are excreted quantitatively.

ARTHUR LOCKE.

THE METABOLISM OF GLYCEROL IN PHLORHIZIN DIABETES. W. H. CHAMBERS and H. J. DEUEL, JR., J. Biol. Chem. **65**:21, 1925.

Glycerol is almost completely converted into glucose in phlorhizinized dogs. The respiratory quotient decreases following the ingestion of the glycerol, indicating that there is no general oxidation except of the two atoms of hydrogen

liberated by each molecule of glycerol in its conversion to glucose. The glycerol induces a sparing of protein metabolism similar to that caused by carbohydrate ingestion.

ARTHUR LOCKE.

BLOOD SUGAR TIME CURVES FOLLOWING THE INGESTION OF DIHYDROXYACETONE. I. M. RABINOWITCH, J. Biol. Chem. **65**:55, 1925.

The ingestion of dihydroxyacetone is followed by a lowering of the blood sugar.

ARTHUR LOCKE.

AN EXTRACT OBTAINED FROM THE EXTERNAL BOVINE PARATHYROID GLANDS CAPABLE OF INDUCING HYPERCALCEMIA IN NORMAL AND THYREO-PARATHYROPRIVIC DOGS. A. M. HJORT, S. C. ROBINSON, and F. H. TENDICK, J. Biol. Chem. **65**:117, 1925.

A hormone is obtained from the lipoid-free portion of fresh, bovine parathyroid glands which relieves tetany and induces hypercalcemia. The hormone is relatively stable.

ARTHUR LOCKE.

VARIATIONS IN THE FASTING BLOOD SUGAR LEVEL AND IN SUGAR TOLERANCE IN RELATION TO THE MENSTRUAL CYCLE. R. OKEY and E. I. ROBB, J. Biol. Chem. **65**:165, 1925.

There is no consistent cyclic variation in the fasting blood sugar level in women. The blood sugar values following glucose ingestion during menstruation suggest an altered functioning of the pancreas at this time.

ARTHUR LOCKE.

THE EFFECT OF CARBON DIOXIDE ON CELLS IN TISSUE CULTURES. JOHN T. BAUER, Bull. Johns Hopkins Hosp. **37**:420, 1925.

Carbon dioxide had a paralyzing effect on the connective tissue cells in vitro, inhibiting the movement of the mitochondria and granules and retarding division greatly in prophase, to a lesser degree in metaphase and anaphase, and only slightly in telophase.

In unstained preparations the cytoplasm, nucleus, and nucleoli became more transparent with carbon dioxide and suggested increased fluidity of the protoplasm.

In preparations stained with neutral red there occurred a slight change in color of the neutral red granules and vacuoles and also some coagulation of the nucleus, which seemed to indicate that the carbon dioxide behaved as an acid.

Carbon dioxide was relatively nontoxic in the amounts used, but could produce death after prolonged use or with increased amounts.

AUTHOR'S SUMMARY.

ACUTE HYPOTENSION OF CEREBRO-SPINAL FLUID FOLLOWING CRANIAL TRAUMATISM. E. STUTZ and P. STRICKER, Ann. Surg. **82**:678, 1925.

In some cases of cranial trauma the pressure of the cerebrospinal fluid is lowered. This hypotension has fairly well defined clinical features more or less in contrast to those of hypertension. The authors report three such cases in which the patients were treated by intravenous injection of distilled water, with resulting rise in spinal fluid pressure and relief of symptoms.

N. ENZER.

MAXIMAL HYPOGLYCEMIA WITHOUT THE USE OF INSULIN. E. GEIGER and L. SZIRTES, Klin. Wchnschr. **4**:1912, 1925.

The injection of colitoxin or of atropin into animals, after cutting the splanchnic nerves, produces a hypothermia and marked hypoglycemia. The blood sugar falls as low as 0.03 to 0.01 per cent, the temperature as low as 36 C., without convulsions. When convulsions occur, they are allayed by the injection of epinephrin, while the blood sugar falls to an even lower value.

ARTHUR LOCKE.

THE PHAGOCYTIC CAPACITY OF THE LEUKOCYTES IN RABBITS WITH VARIED BLOOD ENDOCRINE CORRELATION. R. M. BIERSTEIN and A. M. RABINOVITSCH, Klin. Wchnschr. **4**:2013, 1925.

Castration, thyrectomy and thymectomy cause a lowered phagocytosis in rabbits. Reimplantation of the extirpated glands causes an increase in phagocytosis which, however, does not reach the normal value. The changes in phagocytic capacity are not due to the absence of a definite hormone but to the changes in the entire endocrine correlation.

ARTHUR LOCKE.

THE GENESIS OF EPILEPTIC ATTACKS. F. GEORGI, Klin. Wchnschr. **4**:2053, 1925.

The changes in the colloidal stability of plasma may be distinguished as proteinogenic and ionogenic. Proteinogenic changes in colloidal stability are recognized in the protein increases associated with acute infections, gravidity, and in tumors. Ionogenic changes, due to ionic redistributions, are recognized in epileptic attacks and in hyperventilation. The origin of the epileptic attack is explained as a "coupling of factors": inner secretory disturbances leading to reversible ionogenic fluid changes, which by reversible increases in the permeability of the cell membranes primarily stimulate pathologic cortical cells.

ARTHUR LOCKE.

THE MOTOR AND SECRETORY FUNCTIONS OF THE STOMACH. L. HESS and J. FALTITSCHEK, Wien. klin. Wchnschr. **38**:1232, 1925.

Patients with ulcers of the stomach show no change in the secretory or motor function of the stomach after paravertebral injection of from 5 to 10 cc. of a 1 per cent solution of procaine, made in the seventh thoracic segment. In healthy subjects and in gastric neuroses, the increase in both was constant. It is believed that the lack of reaction in patients with ulcers is due to an organic interruption of nerve conduction.

TEMPERATURE ELEVATION CAUSED BY PRODUCTS OF BACTERIAL AUTOLYSIS. JOSÉ CARRA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **43**:46, 1925.

Filtrates of autolyzed *Staphylococcus aureus* were injected intravenously into rabbits, and variations in temperature were noted. Two effects were found: a fall in temperature, followed by a rise. Depending on the length of time that autolysis had gone on, these two effects varied. In seven day preparations there was no fall, but only a rise in temperature; at twenty-five days both occurred in about an equal degree, and at fifty days the fall alone followed the injection. Two "substances" are suggested as an explanation of these phenomena.

JEAN OLIVER.

RENEWAL OF THE BLOOD. A. LICHTENSTEIN and A. J. L. TERWEN, Deutsch. Arch. f. klin. Med. **149**:102, 1925.

Litchtenstein and Terwen found 135 mg. of urobilin per day and 111 mg. per hundred grams of feces as the average, and 200 mg. per day as the maximum, in the feces of fifteen healthy persons. The excretion varies from day to day. Normal urine contains less than 1 mg. per day. Estimating the amount of blood in a normal adult (70 Kg.) at 3,500 Gm., with a hemoglobin content of 14 per cent, and figuring on the production of 21.1 Gm. of urobilinogen from 21.9 Gm. of hematin (contained in the amount of hemoglobin specified), and on the elimination of 150 mg. of urobilin per day, the whole blood is renewed in 140 days or less (Eppenger concluded, from the secretion of bilirubin, in sixty to forty-three days.) They compare this normal speed of destruction with that of any given subject and call the ratio an index of the "molting" of the blood. Its formula is: $\frac{70}{P} \times \frac{100}{Hb} \times \frac{Ur}{150}$ (P = weight in kilograms; Hb = percentage of hemoglobin; Ur = daily excretion of urobilin in milligrams). Other signs of increased wastage are the supravitally stained substance in more than 0.5 per cent of the erythrocytes, and the increased bilirubinemia.

ON THE CONNECTION BETWEEN ALBUMINURIA AND THE HYDROGEN ION CONCENTRATION IN THE BLOOD AND URINE. INAUGURAL DISSERTATION. ALFRED BJURE, Upsala, 1925.

Using hydrogen ion concentrations determined in the blood from carbon dioxide determinations by means of Hasselbalch's method, and in urine by the nitrophenol method of Michaelis, the author has investigated the relationship of these to various types of albuminuria—albuminuria following exertion, orthostatic albuminuria, albuminuria following eating and diabetic albuminuria. His findings are:

Albuminuria following exertion appears to be due principally to heightened hydrogen ion content of the blood and to a less degree to transient renal congestion. In orthostatic albuminuria the latter cause alone is effective. Diabetic albuminuria is to be explained as the result of the action of acidosis produced by the acetone bodies on the kidneys.

These albuminurias show a manifest similarity in that the excretion of albumin is definitely diminished by the administration of alkali. This effect is frequently most marked in orthostatic albuminuria.

Hence he concludes that all these albuminurias are to be explained on a basis of renal acidosis, either local, as in the case of orthostatic albuminuria, or general, as in the albuminurias following exertion or of diabetes.

Excessive administration of alkali can also result in albuminuria. This is to be explained as resulting from the reverse picture, that of undue diminution of hydrogen ion concentration.

H. E. EGGERS.

THE INFLUENCE OF THE CONSTITUENTS OF THE THYMUS GLAND CELLS ON THE GROWTH OF YOUNG ORGANISMS. Y. MIYAGAWA and K. WADA, Sc. Rep. Govt. Inst. Infect. Dis., Tokio **3**:42, 1924.

Following intraperitoneal injection into young white rats and dogs of the cell constituents of calf's thymus, there is a remarkable increase of weight when small doses (0.05 Gm. per kilogram) are administered; with larger doses (1 to 2 Gm. per kilogram) growth and development are retarded. Control

injections of other organs are without effect except in the case of the thyroid in which, with sufficient doses, growth is retarded. While admitting that these results may be explained as due to the action of specific constituents, the writers believe the main effect to be due to the direct action of the cell constituents, after absorption into the circulation, on the homologous gland — thymus or thyroid — with facilitation or retardation of its function.

H. E. Eggers.

An Experimental Study on the Secretion of Bile. S. Kodama, Sc. Rep. Govt. Inst. Infect. Dis., Tokio **3**:71, 1924.

This article reports the results of the injection of various organ emulsions into dogs with biliary fistulas. Specific results follow the injection of liver cell emulsion in that bile pigment excretion is greatly increased by the injection of minute doses, whereas it is markedly decreased by large doses. Biochemical tests — the dextrose test and the hydrochloric suprarenal test — show acceleration or retardation of liver function with small and large doses, respectively. Similar effect is observed on body weight, small doses of liver emulsion causing an increase and large doses a rapid loss. Blood changes — early lymphocytosis, anemia and final lipemia — are accelerated by the injection. Hepatic degenerative changes both of the parenchymatous cells and in the appearance of cirrhosis were augmented or hastened by the injection. All the foregoing is interpreted as evidence of the direct action on organ cells by the homologous cell constituents.

H. E. Eggers.

Pathologic Anatomy

Neuron Destruction in Postencephalitic Paralysis Agitans. J. Charnley McKinley and Lawrence R. Gowan, Arch. Neurol. & Psychiat. **15**:1 (Jan.) 1926.

In two additional cases of postencephalitic paralysis agitans studied by ordinary histologic methods, minimal changes of the globus pallidus but massive lesions of the substantia nigra were found. Scattered lesions found in other parts of the brains were so insignificant as to require no intensive investigation.

The two foregoing cases and a previously reported case have been studied by micrometric methods in order to evaluate quantitatively the amount of cell destruction in the lenticular region and substantia nigra.

In comparison with the normal cases, no decrease in the number of cells in the putamen or globus pallidus can be demonstrated.

An average decrease in the number of neurons of from 58 per cent to 87 per cent has occurred in the substantia nigra in the three cases.

From these data it appears that the syndrome of paralysis agitans may occur without a significant lesion in the globus pallidus, although this is not intended to mean that the globus pallidus never plays a rôle in parkinsonianism.

The destruction in the substantia nigra seems to be the essential factor in the production of the syndrome, at least in the three cases presented.

Micrometric methods are of great value to the neuropathologist and should be more commonly employed.

Authors' Summary.

Brain Repair. Richard B. Wilson, Arch. Neurol. & Psychiat. **15**:75 (Jan.) 1926.

The needle tracks in two general paralytic brains were studied, one six days after one puncture and the other from seven to eleven and a half months after six punctures. An attempt is made to describe the reparative process.

In the case in which puncture was performed recently, the cellular reaction was rather intense, especially in the more vascular regions. This consisted of small round cells, phagocytic cells and cellular detritus. The degree of the filling in of the wound canals appears to depend directly on the amount of vascularity of the tissue. It is accomplished by connective tissue elements. The connective tissue repair was more advanced in the older canals where rather dense connective tissue cicatrices were found, which blended with the bordering neuroglia fibers. In the deeper white layers the wound canals were incompletely filled in with loose strands of connective tissue, in the meshes of which were many phagocytic cells and considerable cellular detritus. Of interest in the second case is the presence, on the ventricular surface overlying the wound canal, of a dense layer of well preserved red blood cells, seven months after the last injury. Rare giant cells were encountered in the vicinity of the older canals. Glial reaction was manifested by an increase of protoplasm. This reaction was more marked and more expansive in the cortical layers.

AUTHOR'S SUMMARY.

THE EARLY PHASES OF CELL INJURY WITH SPECIAL REFERENCE TO MITOCHONDRIA. J. LORRAIN SMITH, J. Path. & Bact. **28**:627, 1925.

Study was made of the changes that take place in the mitochondria in cloudy swelling and in fatty degeneration. By means of special staining it is shown that cloudy swelling and fatty degeneration begin in damage to the mitochondria. This damage occurred without regard to the agent used and is due to toxic action. The recovery of a cell from degeneration involves a rebuilding of mitochondria, and restoration may take place if the damage has not been too severe.

ERNEST M. HALL.

CHRONIC SUBDURAL HEMATOMA. V. J. PUTNAM, Arch. Surg. **11**:329, 1925.

Subdural hematomas are far more common than they were previously considered to be and must be differentiated from pachymeningitis hemorrhagica. The hematomas are well encapsulated and sometimes bilateral. The interesting feature is the capsule, which consists of a membrane, slightly adherent to the dura, but not to the arachnoid. That portion of the membrane adjacent to the arachnoid is made up of thin, fibrous tissue lined by mesothelium, but that attached to the dura is thicker and consists chiefly of organizing granulation tissue, usually vascular, and in the traumatic cases containing many anastamosing spaces lined by mesothelial cells and usually filled with blood and fibrin. These spaces are absent in pachymeningitis interna, in which Virchow pointed out that the membrane may give rise to hemorrhage and thus form a hematoma. Putnam calls the membrane found in these traumatic cases a reactive pachymeningitis and thinks that this peculiar organization is evoked by the presence of blood and fibrin on the under surface of the dura. Eleven cases are presented in detail and discussed. In a foreword to the article, Cushing ascribes the peculiar greenish color found on the surface of these hematomas to bile pigment derived in situ.

N. ENZER.

CONGENITAL ANOMALIES OF THE INTESTINE; INTESTINAL APLASIA, ATRESIA OF THE RECTUM AND ANUS COMPLICATED BY RECTO-VESICAL FISTULA. R. E. FARR and C. W. BRUNKOW, Arch. Surg. **11**:417, 1925.

These authors report one case of intestinal aplasia and one of atresia of the rectum and anus complicated by rectovesical fistula, and they review the litera-

ture with regard to the former. They tend to favor the developmental theory of formation of aplasia or atresia in preference to adhesions, infections, volvulus and vascular occlusion. More abundant formation of embryonic septums in the duodenum should indicate it as being the most frequent site, but some have found the condition more frequent in the jejuno-ileo region. In the case reported there was a blind ending 75 cm. from the pylorus with a *V* defect in the mesentery and no connection between the separated ends of intestine. They also report a case of anal and rectal aplasia with rectovesical fistula. These are usually associated with other anomalies of the intestinal tract or urinary tract. The etiologic element is a defect failure in the complete development of the urogenital diaphragm. Dependent on the location of the defect, the fistula may be rectovesical, recto-uretheral or rectovaginal.

N. Enzer.

Pulmonary Atelectasis with Special Reference to Massive Collapse of the Lung. E. D. Churchill, Arch. Surg. **11**:489, 1925.

Massive collapse of the lung is a variety of pulmonary atelectasis and probably due to the same etiologic factors, viz.: bronchial obstruction and weakened respiratory force. Nine cases are presented, and common to all of them were weakened respiratory force and bronchial obstruction. Early purulent sputum was present in all postoperative cases, and several of them had a history of previous respiratory infection. The weakened respiratory force may be due to a low physical state or to paralysis or impairment of the respiratory muscles. The right lower lobe was most often affected, and this is attributed to the construction of the bronchial tree which favors gravitation of exudate or secretion to this lobe. Atelectasis most likely does not predispose to pneumonia, nor do emboli appear to be a factor in the etiology. The literature is reviewed.

N. Enzer.

Tuberculosis of Meckel's Diverticulum Associated with Tuberculous Appendix. B. L. Coley, Arch. Surg. **11**:519, 1925.

Coley has been able to collect nine cases in the literature of tuberculosis of Meckel's diverticulum, which he summarizes and now adds one of his own, which was associated with tuberculosis of the appendix. Pathologic conditions occurring in Meckel's diverticulum are enumerated, and the pathogenesis of enteric tuberculosis is briefly discussed.

N. Enzer.

Unusual Conditions in the Duodenum and Their Significance. Membraneous Obstruction of the Lumen, Diverticula and Carcinoma. G. W. Nagel, Arch. Surg. **11**:529, 1925.

One case of membranous obstruction is reported, and the summary of seven cases found in the literature. The membrane in this case was above the ampulla of Vater. Twenty-six diverticula of developmental origin are presented, and their origin, pathology and the clinical aspects are discussed. The majority were associated with duodenal ulcers. Three cases of secondary involvement of the duodenum by carcinoma and nine cases of apparently primary carcinoma are described.

N. Enzer.

INTRACRANIAL HEMORRHAGE IN THE NEWBORN. W. SHARPE and A. S. MCCLAIRE, Surg., Gynec. & Obst. **41**:583 (Nov.) 1925.

This is a report of the fifth series of 100 cases of new-born babies on whom a lumbar puncture was performed within forty-eight hours after birth. In this series blood-tinged spinal fluid was found in six. The authors believe that intracranial hemorrhage is a much more common sequel to birth trauma than previously supposed, and the clinical sign may be meager, prolonged drowsiness and difficulty in nursing being most common. They stress the remote effects of these hemorrhages, and advocate early lumbar tap to establish drainage.

PRIMARY SPINDLE CELL SARCOMA OF MECKEL'S DIVERTICULUM. G. W. CRILE and N. V. PORTMAN, Surg., Gynec. & Obst. **41**:615 (Nov.) 1925.

Seven cases of malignant tumor in Meckel's diverticulum have been reported, three of which were sarcomas. The authors report a spindle cell sarcoma in a Meckel's diverticulum discovered at operation for intestinal obstruction.

N. ENZER.

EXTRADURAL SPINAL MENINGEAL HEMORRHAGE. J. REID and J. KENNEDY, Brit. M. J. **2**:946, 1925.

Beginning three days after a slight bruise of the left arm, the patient (woman) developed flaccid paralysis, first in the legs and later in the arms. After death there was found an extradural hemorrhage along the whole length of the cord up to the level of the third cervical vertebra. There was no injury or disease of the spinal column, no obvious lesions of the spinal meninges, and the source of the bleeding was not found. Tuberculous foci were present in the tubes, the lungs and the meninges in the occipital region.

RIEDEL'S CHRONIC THYROIDITIS: WITH A REPORT OF SIX CASES AND A CONTRIBUTION TO THE PATHOLOGY. A. F. BERNARD SHAW and R. P. SMITH, Brit. J. Surg. **13**:93, 1925.

The authors present six cases of Riedel's disease. All occurred in women between the ages of 32 and 58 years. The view is concurred in that the picture of an intense round cell infiltration with follicle formation and that of a diffuse cirrhosis present early and late stages of the same process. Three of the present group showed the early type of change. In the remaining three the changes were advanced, and serious pressure had been produced. The authors are inclined to regard the condition as a granuloma. Extracapsular extension was found to occur early, and in one case of the present group was extensive enough to prevent operation. In another case of the series, in which the patient was admitted as having a typical Addison's disease the thyroid was found to be moderately enlarged and hardened, and at necropsy both thyroid and suprarenals showed the changes characteristic of an early stage of Riedel's disease. A review of the literature from 1896 to 1924 revealed reports of only twenty-three cases, which are tabulated in detail.

LAWRENCE JACQUES.

EXTRAVASATION OF BILE. ZACHARY COPE, Brit. J. Surg. **13**:120, 1925.

Bile is extravasated in the great majority of cases into the peritoneal cavity, but may find its way into the retroperitoneal tissues, either by rupture of portions of the biliary tract uncovered by peritoneum, or secondarily, by an

intraperitoneal collection bursting into the tissues behind the peritoneum. Two cases of retroperitoneal rupture are described. The author is of the opinion that extravasation occurs always through a perforation, although the latter may not always be found. It is suggested that the glands of Luschka may provide a ready channel for the spread of bacterial infection and for leakage of bile.

LAWRENCE JACQUES.

APLASTIC AND PSEUDO-APLASTIC ANEMIA. E. GREPPI, Arch. di pat. e clin. med. **4**:326, 1925.

Some believe that pernicious and aplastic anemia are the same disease in different stages. Greppi regards them as different, and divides them into three classes: (1) pernicious anemia, in which the color index is higher than 1 with constant achylia, atrophic glossitis, moderate leukopenia, petechial hemorrhages, urobilin in large amounts, high bilirubin content in the blood serum and hyperplastic marrow; (2) aplastic anemia, in which the color index is less than 1 and achylia is often present with gingivitis, stomatitis, marked leukopenia with neutrophilopenia, frequent hemorrhages which tend to be diffuse, no urobilin, low bilirubin in the blood serum and hypoplasia of the marrow; (3) pseudo-aplastic anemia — typical forms of pernicious anemia that may present some of the characteristics of aplastic anemia, such as color index of less than 1 together with a picture of marked blood reduction, but they are differentiated from aplastic anemia by the fact that they are accompanied by high bilirubin content; in other words, the point of differentiation is based on the presence or absence of hemolysis.

The author reviews the literature and illustrates his points by clinical cases.

A. S. GIORDANO.

ON THE VITAL AFFINITY OF NEUTRAL RED AT A DISTANCE. A. H. ROFFO, Bol. d. Inst. de med. exper. **1**:681, 1925.

The affinity of neutral red for living tissue is shown by the following experiment: If one places pieces of tissue in the middle of a tube of culture medium, with a drop of neutral red solution in the bottom of the tube, the tissue becomes colored while the medium remains clear.

B. R. LOVETT.

A CONTRIBUTION TO THE CIRCUMSCRIBED DEPOSITION OF CALCIUM IN THE SKIN. SEICHI HIDAKA and ICHIRO OGATA, Acta dermat. **6**:487, 1925.

The circumscribed deposition of calcium in and under the skin as a single symptom without secondary change in the epithelium is seldom seen. According to Guhrauer, the characteristics are: the occurrence only on the fingers, the presence of blackish pits from which chalky granules escape, marked sclerodermatous changes in the skin, sometimes with pigmentation and telangiectases, cyanosis of the hands and occurrence chiefly in women. In the cases reported, two in women and three in men, the granules were usually found beneath the skin of the arm, never perforating it. Histologically, a granule or stone consisted of several irregular masses of calcium which seemed to be present on the degenerated collagenic fibers and protoplasm of the connective tissue cells. There was a slight zone of reaction and no change in the overlying corium or epidermis.

B. R. LOVETT.

TWO CASES OF PARADOXIC EMBOLISM BY MEANS OF THE DUCTUS ARTERIOSUS. J. J. MOSER, Rev. méd. de la Suisse Rom. **45**:532, 1925.

Paradoxic embolism so-called because of the appearance of emboli in peripheral arteries from an origin in the peripheral veins, is explained usually as dependent on a persistent interauricular opening. In the cases here described, on the contrary, the emboli are thought to have passed through a patent ductus arteriosus.

G. B. RHODES.

ACROCEPHALOSYNDACTYLISM. J. DE BRUIN, Nederlandsch Tijdschr. v. Geneesk. **2**:2380, 1925.

De Bruin gives an illustrated description of two personal cases of the set of malformations in head, hands and feet to which Apert called attention in 1906, labeling it acrocephalosyndactylia. There are about thirty-three cases on record, none with familial or hereditary features. The prognosis as to life seems to be favorable, but vision is threatened, as in steeple skull. On account of the huge, rounded, protruding skull above the level of the eyes, the exophthalmos and the deformed hands, the education of these children is generally neglected, but otherwise they seem mentally normal; two were idiots.

BEITRAG ZUR KENNTNIS DER AKUTEN PANCREASNEKROSE. STUART RITTER VON LINHARDT, Frank. Ztschr. f. Path. **33**:16, 1925.

Linhardt concludes that the writings of the past fifty years indicate that fat necrosis is not an idiopathic disease but a symptom of pancreatic disease, also that the cause of death is due to autointoxication. No agreement has been reached, however, concerning the origin of pancreas necrosis. To produce autodigestion of the pancreas an active ferment is liberated. The origin of the selfdigestion and what causes activation of the ferment are not agreed on. From a consideration of his own cases and many cases from the literature Linhardt believes that although the causes of necrosis of the pancreas may be of different kinds, the real cause is a disharmony of the vegetative nervous system of the individual. The latter condition may be constitutional or it may be acquired through certain diseases. On the basis of Westphal's investigations he believes that the underlying cause might be a sympathetic hypotonic motility neurosis.

ERNEST M. HALL.

ARSPHENAMINE AND THE RETICULO-ENDOTHELIAL SYSTEM. DEL BAERE, Wien. klin. Wchnschr. **38**:1123, 1925.

Intravenous injections of neo-arsphenamine retards the disappearance of congo red from the blood, due, it is concluded, to blocking of the reticulo-endothelial cells.

RECOGNITION OF SPONTANEOUS RUPTURE OF THE EPIGASTRIC ARTERY. KASPER BLOND, Wien. klin. Wchnschr. **38**:1352, 1925.

A spontaneous hematoma of the abdominal wall is usually the result of the breaking of the superior or inferior epigastric artery whose wall has been injured by an acute or chronic affection. In its etiology and classification this condition has no relation to traumatic rupture of the rectus abdominalis muscle. Clinically it is differentiated by the absence of separation of the

muscle ends. Genetically the injuries of the vessel walls are due to infectious diseases or arteriosclerosis. All conditions that increase intra-abdominal pressure may be considered as contributing factors.

AUTHOR'S SUMMARY.

THE PATHOGENESIS OF SO-CALLED SPOTTED SPLEEN (FLECKMILZ). MEURET, Beitr. z. path. Anat. u. z. allg. Path. **73**:525, 1925.

Meuret reports two cases of multiple necroses of the spleen, a condition which Feitis described in 1921 as "Fleckmilz." In both cases the underlying condition was chronic interstitial nephritis of arteriosclerotic type. The condition in the spleen was one of multiple, small, nonseptic infarction necroses. Meuret interprets the lesions as the result of arteriosclerosis of the terminal splenic arterioles, leading to secondary thrombosis, with resultant infarction. He disagrees with Wilton, who has recently claimed that such multiple necroses of the spleen are always toxic in origin, the thrombosis being secondary to the necrosis. Meuret admits, however, that in certain cases, such as those of Geipel and of Matthias, who reported multiple necroses of the spleen in eclampsia, the infarction and necrosis may be due to toxic vascular spasm.

O. T. SCHULTZ.

SPINA BIFIDA AND AMNIOTIC ADHESION. H. FERIZ, Virchows Arch. f. path. Anat. **257**:503, 1925.

A child with spina bifida also had marked congenital elephantiasis of a finger. The latter anomaly was due to an amniotic adhesion. From the combination of the two anomalies present the author concludes that amniotic adhesions and bands are the result of the same factors which cause the so-called endogenous malformations, or are the result of the latter.

O. T. SCHULTZ.

ACUTE EXTERNAL SPINAL PACHYMENINGITIS. A. SCHMALZ, Virchows Arch. f. path. Anat. **257**:521, 1925.

During the past five years ten cases of acute external spinal pachymeningitis have been reported, the impression being conveyed that this is a new and not previously described disease process. Schmalz, however, shows that the condition has been known for a long time, and he was able to find sixty-four reported cases; of these, he tabulates and abstracts forty-one, the first being credited to Morgagni. He adds two cases of his own. The inflammatory process is an acute purulent one which is secondary to infection elsewhere, but only rarely to vertebral osteomyelitis. The pathogenesis, pathology, anatomy, symptomatology and course, diagnosis, prognosis and treatment of the condition are discussed. This is the type of complete and valuable report which should warn against the publication of cases as "new and hitherto undescribed" conditions.

O. T. SCHULTZ.

RÔLE OF INFECTION AND VESSEL WALL INJURY IN THROMBOSIS. T. SATO, Virchows Arch. f. path. Anat. **257**:561, 1925.

Under the direction of Lubarsch, Sato undertook an experimental investigation of the rôle of infection and of changes in the artery wall in thrombosis. To produce varying degrees of vessel wall change, aseptic autotransplantations, homoiotransplantations and heterotransplantations of arterial segments from

1 to 4 cm. long were made into the femoral or carotid arteries of dogs. To determine the effect of infection, the suture material was contaminated with staphylococci in a series of similar transplantations. Aseptic autotransplantations and homoiotransplantations did not lead to thrombosis unless the narrowing of the lumen of the vessel was extreme. In the heterotransplantation experiments necrosis of the transplant was associated with thrombosis, and necrosis of the vessel was believed to be the chief factor in causing thrombosis. Infection was an important accessory factor, but in the absence of necrosis required other conditions, such as slowing of the circulation through a narrowed vessel, to established thrombosis.

O. T. Schultz.

The Relation of Osteomalacia and Rickets to Ostitis Fibrosa. F. J. Lang, Virchows Arch. f. path Anat. **257**:594, 1925.

Lang reports a microscopic study of the bones from nine cases of osteomalacia and ten cases of rickets, the purpose of the investigation being an attempt to evaluate the fibrosis of the marrow and of the trabeculae of the spongy bone and to determine the relation of osteomalacia and rickets to ostitis fibrosa. He concludes that the primary condition in both osteomalacia and rickets is defective calcification of the bone, as the result of which the bones are subjected to static, mechanical and functional factors which act as a stimulus to proliferation of connective tissue, which often has a mucoid character. The fibrosis is a secondary and nonspecific change in both osteomalacia and rickets, and either condition may result in ostitis fibrosa.

O. T. Schultz.

On the Significance of the Germ Center in Lymph Follicles. I. Kozumi, Sc. Rpt. Govt. Inst. Infect. Dis., Tokio **3**:83, 1924.

From the comparative biologic study of lymphadenoid tissue the writer concludes that the germ center of the lymph follicle represents a real developmental stage, but one that frequently shows in addition the degenerative phenomena which Hellman believes it solely represents.

H. E. Eggers.

Pathologic Chemistry

The Lipoid Partition in Blood in Health and in Disease. B. L. Oser and W. G. Karr, Arch. Int. Med. **36**:507, 1925.

Since no constant balance between cholesterol and "lecithin" appears to exist in normal blood, the theory of an antagonistic relation between these substances does not receive the support of the authors.

Analyses of the blood in a series of pathologic cases show that considerable variation in the cell concentration of lipoid substances may occur, particularly in blood of low cell content.

S. A. Levinson.

Changes in the Composition of the Urine After Muscular Exercise. D. W. Wilson, W. L. Long, H. C. Thompson and S. Thurlow, J. Biol. Chem. **65**:755, 1925.

There is a decrease in urine volume, an increase in hydrogen ion concentration, and in acid and ammonia excretion following exercise. The elimination of phosphates rises while that of chlorides decreases.

Arthur Locke.

ON THE PREPARATION OF HAEMATOPORPHYRIN FROM CARBON MONOXIDE HAEMOGLOBIN. HANS SMETANA, Bull. Johns Hopkins Hosp. **37**:408, 1925.

A modification of the Arnold method for the preparation of hematoporphyrin from carbon monoxide hemoglobin is proposed. By this method comparatively pure hematoporphyrin preparations can easily be obtained.

THE INFLUENCE ON PREGNANCY UPON THE LIPOIDS OF THE BLOOD. M. TYLER and F. P. UNDERHILL, J. Biol. Chem. **66**:1, 1925.

The ratios of lecithin to cholesterol and of cholesterol esters to cholesterol in whole blood remain fairly constant during pregnancy. The former is at all times within the normal limit for that value in nonpregnant women. The latter is increased. Cholesterol, cholesterol esters and lecithin increase gradually until term, when each is approximately 33 per cent higher than at three months. The average value for the total ether extract at term is approximately 50 per cent higher than the nonpregnant value and 30 per cent higher than the value at three months. The values for the ether extract and for the individual lipoids remain high during the first two weeks of the puerperium.

ARTHUR LOCKE.

THE SOLUBILITY OF TERTIARY CALCIUM PHOSPHATE IN CEREBROSPINAL FLUID. L. E. HOLT, JR., J. Biol. Chem. **66**:23, 1925.

Tertiary calcium phosphate is less soluble in cerebrospinal fluid than in blood serum.

ARTHUR LOCKE.

THE MAGNESIUM AND CALCIUM CONTENT OF THE BLOOD AND BLOOD PLASMA OF TUBERCULOUS PATIENTS. E. W. SCHOENHEIT, Am. J. M. Sc. **170**:689, 1925.

The magnesium content of the blood plasma of normal and tuberculous persons is from 0.018 to 0.026 mg. per cubic centimeter. For whole blood the variation is from 0.031 to 0.038 mg. per cubic centimeter. Changes in the magnesium content of the blood are not associated in any regular way with disease.

ARTHUR LOCKE.

STUDIES ON THE RELATIONSHIP OF THE CHEMICAL CONSTITUENTS OF BLOOD AND CEREBROSPINAL FLUID. LAWRENCE S. KUBIE and GERTRUDE M. SHULTS, J. Exper. Med. **42**:565, 1925.

If due allowance is made for the slow rate of elaboration of cerebrospinal fluid and for the time that it takes for newly formed fluid to emerge from a needle in the cisterna, the amount of sugar, chloride, and nonprotein nitrogen in the fluid seems to follow in a general way their concentrations in the blood stream.

It is equally evident, however, that for any substance other factors besides its concentration in the blood stream play a part in its distribution between blood and cerebrospinal fluid.

AUTHORS' SUMMARY.

THE EFFECT OF ETHYL URETHANE ANESTHESIA ON THE ACID-BASE EQUILIBRIUM AND CELL CONTENTS OF THE BLOOD. JAMES A. HAWKINS and JAMES B. MURPHY, J. Exper. Med. **42**:609, 1925.

When anesthesia is produced in rabbits or rats by injections of ethyl urethane, the carbon dioxid content and p_H of the whole blood of the animal

are more or less rapidly increased to a point where there is a marked uncompensated alkalosis which reaches its maximum at twenty-four hours and persists for forty-eight hours. The increase in the carbon dioxid content and p_H of the whole blood is accompanied by a decrease in the circulating lymphocytes and an increase in the polymorphonuclear leukocytes.

AUTHORS' SUMMARY.

LACTIC ACID IN MAMMALIAN CARDIAC MUSCLE. I. THE STIMULATION MAXIMUM. L. N. KATZ and C. N. H. LONG, Proc. Roy. Soc. **99**:8, 1925. II. THE RIGOR MORTIS MAXIMUM AND THE NORMAL GLYCOGEN CONTENT. H. J. G. HINES, KATZ and LONG, Ibid. **99**:20, 1925.

The heart, unlike skeletal muscle, is dependent on its contemporary oxygen supply and fails rapidly in its absence. The mean value of the lactic acid stimulation maximum is two-thirds less. This is because heart muscle is less well buffered and its critical p_H less acid.

A lack of lactic acid precursor is not the cause of the relatively low stimulation maximum of lactic acid in the heart. While the glycogen content of the heart is much less than that of skeletal muscle, the greater portion of lactic acid precursor is in some other form. The rigor mortis or caffeine rigor maximum of lactic acid in the heart is only half that in skeletal muscle.

ARTHUR LOCKE.

HYDROLYSIS OF PHOSPHORIC ESTERS BY THE KIDNEY IN VIVO. F. EICHHOLZ, R. ROBINSON and L. BRULL, Proc. Roy. Soc. **99**:91, 1925.

The urinary phosphates are normally derived from the organic phosphates of the serum by a process of hydrolysis in the cells of the kidney under the action of a kidney enzyme.

ARTHUR LOCKE.

Microbiology and Parasitology

A STUDY OF RABIES WITH REFERENCE TO A NEURAL TRANSMISSION OF THE VIRUS IN RABBITS, AND THE STRUCTURE AND SIGNIFICANCE OF NEGRI BODIES. ERNEST W. GOODPASTURE, Am. J. Path. **1**:547, 1925.

Rabbits can be infected with rabies by inoculating street virus into the right masseter muscle. A distinction is made between Negri and "lyssa" bodies, both of which are present in the motor nucleus of the fifth nerve and in the central nervous system, most marked, however, on the side of the masseter injected. The lyssa bodies are thought to result from changes in the neurofibrillar substance of ganglion cells, while Negri bodies result from accumulation of neurofibrillar material about the products of mitochondrial degeneration, which is regarded as specific for rabies. Goodpasture does not believe that the virus of rabies has been demonstrated microscopically.

RESEARCHES ON VACCINE VIRUS IN VITRO WITH SPECIAL REFERENCES TO ITS AFFINITY FOR NERVE TISSUE. NORIMASA HIRANO, Am. J. Path. **1**:635, 1925.

Vaccine virus has an affinity for the central nervous system but almost no affinity for the kidney in vitro, the latter having a deleterious effect on the virus. Vaccine virus has also an affinity for testicular tissue, but this is

less marked than its affinity for nervous tissue. Vaccine virus survives in nervous tissue immersed in fluid medium after dying out in the latter.

Vaccine virus in culture medium containing spinal cord produces a more marked reaction on the skin of rabbits than the virus in medium containing kidney, although the difference is by no means sharp; however, there appears to be almost no difference in the effect of spinal cord and testicle on the virus suspended in the medium.

The vaccine virus emulsified with spinal cord causes more marked inflammatory reaction than control glycerinated virus. Therefore, it would appear that the spinal cord of a normal rabbit is favorable to the growth of the virus and tends to increase its virulence.

Vaccine virus appears to be incapable of migrating along the spinal cord in vitro.

AUTHOR'S SUMMARY.

A BACILLUS OF THE PARATHYPHOID GROUP. HOWARD ANDERSON MCCORDOCK, Bull. Johns Hopkins Hosp. **37**:412, 1925.

A bacillus of the paratyphoid group, apparently unencountered by previous investigators, is reported.

Culturally it is similar to the other parathyphoids but can be differentiated from them by its low avidity for rhamnose, failing to ferment this sugar in twenty-four hours, and the absence, or only slight production, of gas in all carbohydrates except xylose.

Agglutination tests leave no doubt concerning its individualtiy, and agglutinin absorptions sharply separate it from the other parathyphoid types.

The organism is pathogenic for mice, rabbits and guinea-pigs, but especially for rats.

For the bacillus described the name *Salmonella muriotitis* is proposed.

AUTHOR'S SUMMARY.

MUCOR INFECTION OF LUNGS FOLLOWED BY PULMONARY TUBERCULOSIS. H. FREED and J. B. WEBB, U. S. Veterans' Bureau Med. Bull. **1**:7, 1925.

The case reported presented an initial pulmonary and laryngeal infection with a pathogenic fungus belonging to the hyphomycetes group, none of which are reported in the literature. The specific pathologic process subsided and *Mucor corymbifer* disappeared from the sputum. Subsequently, there was an insidious development of pulmonary tuberculosis.

STUDIES ON THE ETIOLOGY OF JAGZIEKTE. II. ORIGIN OF THE EPITHELIAL PROLIFERATIONS, AND THE SUBSEQUENT CHANGES. E. V. COWDRY, J. Exper. Med. **42**:335, 1925.

The epithelial proliferations which are so typical of jagziekte are chiefly of alveolar origin. They appear in areas of infiltration and exudation identical histologically with those occurring in sheep which are to all appearances normal but which are derived from flocks in which the disease is endemic. They become extensive and atypical in structure, but they never rise to metastases, even to the adjacent lymph glands. The primary infiltration of the interalveolar tissue continues and may lead to fibrosis and extensive consolidation, or leukocytes may accumulate in large numbers, penetrate into the alveoli, and form areas of acute pneumonia. In fairly advanced cases of jagziekte it is

common to find many stages of the reaction in one and the same lung. While it is possible that the disease may be due to a single and specific virus, and the epithelial lesions are certainly of a special character, the pathologic complex as a whole is such as might be caused by a variety of predisposing and exciting factors operating over a considerable periods of time.

STUDIES ON THE BACTERIOPHAGE OF D'HERELLE. II. EFFECT OF ALCOHOL ON THE BACTERIOPHAGE OF D'HERELLE. JACQUES J. BRONFENBRENNER and CHARLES KORB, J. Exper. Med. **42**:419, 1925.

When bacteriophage is precipitated by alcohol at room temperature its activity rapidly and progressively decreases until it is totally destroyed, between 6 and 24 hours after exposure. If the precipitation is carried out at 7 C., the destruction of lytic activity is considerably slower; measurable traces may be detected even after four weeks' exposure to alcohol. Although the major portion of the lytic activity is found in the precipitate, the supernatant alcohol carries a measurable amount of lytic principle which remains active for several days.

In all cases the residual lytic activity was found to be transmissible in series. In no instance were the authors able to observe the nontransmissible action ascribed by d'Herelle to the enzyme. The persistence of traces of active principle after many weeks of exposure to alcohol at low temperature is not found to be due to the existence in the original filtrate of a fraction relatively resistant to the effect of alcohol.

The inactivation of bacteriophage by alcohol seems, therefore, analogous to the alcoholic inactivation of certain enzymes and toxins.

COMPARATIVE STUDIES OF THE ACTION ON THE PNEUMOCOCCUS OF BILE ACIDS AND UNSATURATED FATTY ACIDS FOUND IN BILE IN THE FORM OF SOAPS. ANTHONY KOZLOWSKI, J. Exper. Med. **42**:453, 1925.

Ox bile contains the soaps of unsaturated higher fatty acids not only with one, but also with two and more than two double bonds, in a dilution of about 1:600. These substances, when isolated from bile, exert an antiseptic action on the pneumococcus in a dilution of approximately 1:50,000, and kill the organism in a dilution of 1:5,000 in approximately one hour. As their action is about 100 times stronger than that of the conjugated bile acids, their presence in bile should be considered, whereas hitherto it has been entirely overlooked, not only by bacteriologists, but by physiologists as well. Since the soaps of unsaturated fatty acids dissolve the pneumococcus cell in broth culture, Neufeld's conclusion (that they do not dissolve pneumococci) is no longer valid.

AUTHOR'S SUMMARY.

BIOLOGY OF BACTERIUM LEPISEPTICUM. II. THE STRUCTURE OF SOME IRON COMPOUNDS WHICH INFLUENCE THE GROWTH OF CERTAIN BACTERIA OF THE HEMOPHILIC, ANAEROBIC, AND HEMORRHAGIC SEPTICEMIA GROUPS. LESLIE T. WEBSTER AND OSKAR BAUDISCH, J. Exper. Med. **42**:473, 1925.

Inorganic iron substances of known chemical structure have been tested for their ability to function as the X factor (biocatalyst) in the growth of bacteria of the hemophilic, anaerobic and hemorrhagic septicemia groups.

Each iron compound possessing this biocatalytic activity showed oxygen-absorbing and peroxidase properties.

AUTHORS' SUMMARY.

STUDIES ON THE BACTERIOPHAGE OF D'HERELLE. III. SOME OF THE FACTORS DETERMINING THE NUMBER AND SIZE OF PLAQUES OF BACTERIAL LYSIS ON AGAR. JACQUES J. BRONFENBRENNER and CHARLES KORB, J. Exper. Med. **42**: 483, 1925.

The fact is confirmed that lytic principle is distributed in active solution in a state of indivisible units. This permits its quantitative evaluation by serial dilution, as well as by plating on agar. The latter method, however, often gives readings considerably lower than those obtained by the broth dilution method of titration. By varying the concentration of agar, it has been possible to show that the discrepancy is due to adsorption of the lytic agent on agar. When the concentration of the latter is increased from 0.3 per cent. to 2.5 per cent., the number of plaques of lysis is reduced more than 100-times. At the same time the average size of the plaques also decreases approximately to one-tenth of the original.

The size, as well as the number of plaques, has been found to depend also on the condition of the culture employed in titration. Thus, when the culture exposed to the action of lytic agent is composed of young susceptible bacteria, the greater the concentration of bacteria, the smaller the plaques.

When the culture is composed partly of young and partly of old susceptible bacteria, both the size and the number of the plaques are diminished with the increase in the relative concentration of old bacteria. On the other hand, presence of resistant bacteria in the culture does not affect the size or the number of the plaques so long as the relative concentration of susceptible bacteria in the culture is sufficient to allow formation of them. The plaques appearing in the presence of a high concentration of resistant variants in the culture are relatively indistinct owing to overgrowth.

Under carefully controlled conditions, the size of plaques is found to be determined by the character of the lytic filtrate. Thus in the case of lytic agents which act on more than one bacterial species, the size of the plaques remains constant, irrespective of the bacterial substratum used for the production of the active filtrate.

AUTHORS' SUMMARY.

STUDIES ON REGENERATION OF BACTERIOPHAGE. I. THE INFLUENCE OF PARTIAL ANAEROBIOSIS UPON REGENERATION OF A HIGHLY DILUTED LYTIC PRINCIPLE. GEORGE SHWARTZMAN, J. Exper. Med. **42**:507, 1925.

The regeneration of an extreme dilution of bacteriophage in a large volume of broth, as described by Gratia and DeKruif, is due to the influence of partial anaerobiosis on the regeneration of the principle.

The influence of partial anaerobiosis on regeneration of an extremely diluted bacteriophage was investigated in relation to different factors with the following results.

$\frac{\text{Surface area}}{\text{Total volume}}$ ratio $= 0.5$ expresses the degree of anaerobiosis necessary for regeneration of an extreme dilution of the bacteriophage. An increase in this ratio interferes with regeneration.

The regeneration of the highly diluted bacteriophage under partial anaerobiosis begins definitely at the third hour of bacterial growth and is completed after about the sixth hour.

To obtain the full regeneration of an extreme dilution of the bacteriophage it is sufficient to restrict for one hour the supply of air to a culture containing it, providing that this restriction be produced within the first three hours of the bacterial growth.

AUTHOR'S SUMMARY.

STUDIES ON BRUCELLA (ALKALIGENES) MELITENSIS. II. THE NOMENCLATURE OF THE MELITENSIS-ABORTUS GROUP OF BACTERIAL ORGANISMS. ALICE C. EVANS, Hyg. Lab. Bull. no. 143, 1925, p. 27.

The organism of Malta fever, although named *Micrococcus melitensis* by Bruce who first isolated it, was later described as a rod rather than a coccus, and called by Jordan and others, *Bacillus melitensis*. The Society of American Bacteriologists, however, restricted the name *Bacillus* to aerobic spore-bearing rods, and classified the non-spore-bearing pathogenic rods under the genus *Bacterium*. So *Micrococcus*, or *Bacillus melitensis* became *Bacterium melitensis*. Then, both *Bacterium melitensis* and the bacillus of contagious abortion, now *Bacterium abortus* (not abortum), whose close relationship had already been observed and confirmed, were recognized to differ considerably from the type species of the genus *Bacterium*, and for them a new generic name *Brucella* was proposed.

There were then two new classifications for this melitensis — abortus group, for they were already included, by its very definition, in a genus *Alcaligenes* described by Castellani and Chalmers, who however, left *"Micrococcus melitensis"* unclassified generically because of its questioned bacillary or coccoidal form. *Alcaligenes* by the law of priority should be the accepted name, but only if "fecalis" the type species of this genus, and the melitensis — abortus organisms can be considered cogeneric. Differences of tissue invading power, of size and of action on nitrates exist and may be judged too pronounced for generic unity. The name *Brucella* must then be accepted, with the type species melitensis, whose general description allows the inclusion of the several closely related organisms. There seems to be no good reason for a division into separate species since the serologic reactions of the eight groups unite them into an "intergrading series," and only by the serologic behavior can the groups be differentiated.

To avoid confusion with B. for *Bacillus* the abbreviation Br. is proposed for *Brucella*. The point is also well made that the first time that a name appears in any paper it should be written in full.

E. B. PERRY.

NATIVE CASE OF INFESTATION BY THE FISH TAPEWORM, DIPHYLLOBOTHRIUM LATUM. M. W. LYON, J. A. M. A. **86**:264 (Jan. 25) 1926.

This case from South Bend, Ind., is believed to be the ninth native case of infestation with the fish tapeworm in the United States.

Infestation with the fish tapeworm may occur at a very early age; in the present case earlier than 4 years and in cases reported by others as early as 2 years.

Infestation in the present case appears to have been an accident or else young children are more susceptible than adults, as an older brother in this case and four adults all eating the same fish were unaffected.

A person harboring a fish tapeworm may expel about 1,000,000 ova daily. Ova do not develop readily under laboratory conditions.

The food requirements of a tapeworm must be considerable when it is realized that the worm can produce germ cells of both sexes at the rate of about a million each twenty-four hours. In the average patient this is probably well taken care of by that "factor of safety" which impels most persons to eat more than is really needed for immediate needs.

A person harboring a fish tapeworm may show almost no symptoms caused by its presence, and if the worm does not show evidence of disintegration there may be no essential change in the blood picture from normal.

The spontaneous appearance of the parasite in this case during an attack of scarlet fever is interesting in showing the tendency of a parasite to leave its host when the normal environment of the parasite becomes altered.

Continued pollution of Great Lakes waters by sewage will probably cause the fish tapeworm to become a common parasite in the northern Middle West. South Bend sewers empty into the St. Joseph River, eventually reaching Lake Michigan.

MADURA FOOT (MYCETOMA): THE BLACK GRAIN VARIETY IN A NATIVE AMERICAN. J. A. GAMMEL, HAGOPE MISKDJIAN and HARVEY S. THATCHER, Arch. Dermat. & Syph. **13**:66 (Jan.) 1926.

Report is made of an infection with the granuloma maduromycosis (mycetoma) in a native American (Mexican) from Texas. This is the twenty-first case reported from the United States and the eleventh from Texas. The infection was of the black grain variety—the first thus far reported in a native American and the second black grain infection reported on the North American continent.

All attempts at animal inoculations were negative. Monkeys (*Macacus rhesus*), rabbits, guinea-pigs, white rats, white mice and pigeons were used.

AUTHORS' SUMMARY.

MORPHOLOGICAL AND PHYSIOLOGICAL VARIATIONS IN THE DESCENDANTS OF A SINGLE DIPHTHERIA BACILLUS. MINOT J. CROWELL, J. Bact. **11**:65, 1926.

Morphologic types of the diphtheria bacillus have no hereditary significance and have no relation to virulence. The descendants of toxic diphtheria organism may be either toxic or nontoxic. The nontoxic strains are direct mutations from toxic strains. The nontoxic strains are permanently nontoxic.

The foregoing conclusions are based on the study of pure line strains obtained by the isolation of a single organism.

AUTHOR'S SUMMARY.

A CASE OF GONOCOCCUS SEPTICAEMIA. LOUIS A. SIEGEL, Bull. Buffalo Gen. Hosp. **3**:66, 1925.

The case presented resembles those observed by Achard and Monzon and by Bloch and Hebert, especially as regards the eruption. The eruptions frequently associated with gonorrheal infections are said to be of an urticarial type. In this case, as well as in those of the authors named above, the eruption was pleomorphic, in places papulopustular and of a general hemorrhagic character as sometimes seen in generalized meningococcic infections. This form of eruption is particularly rare, and seems sufficiently important to place this case on record.

AUTHOR'S SUMMARY.

RELATIONSHIP OF ENTERITIDIS-PARATYPHOID B. INFECTIONS TO HYPERGLYCEMIA IN RABBITS. MAUD L. MENTEN and HELEN M. MANNING, J. Infect. Dis. **37**:400, 1925.

Rabbits subjected to adverse environmental conditions develop hyperglycemia. Coincident with a marked hyperglycemia, cultures of organisms of the

enteritidis-paratyphoid B group may be recovered from organs of rabbits, which likewise show characteristic morphologic changes.

Similar pathologic conditions can be produced by the injection of killed or living organisms of this group.

Hydropic degeneration in the islets of Langerhans in the rabbit is present only when the hyperglycemia is of prolonged continuous duration.

AUTHORS' SUMMARY.

INFLUENZA STUDIES. XX. IDENTIFICATION OF FIXED TYPE PNEUMOCOCCUS CARRIERS. WILLIAM S. SHARP and ELSIE URBANTKE, J. Infect. Dis. **37**:437, 1925.

The technical methods commonly used for the typing of pneumococci in infected sputum are not suited for determining the presence of virulent pneumococci in healthy carriers. Pneumococci of a given type are readily obscured by the more abundant members of the throat flora. Dependable methods of separation from these others, and of subsequent identification, are too laborious for use in extended studies. A new relatively short method is therefore outlined by which it is possible to determine the presence of fixed type pneumococci without isolating them.

The secretion to be tested for the presence of these organisms is streaked over a blood-agar plate. All green zone colonies developing on the plate are transferred to a tube of dextrose blood broth and incubated. The resulting culture is withdrawn from over the blood cells and treated for twenty minutes —at 42 C.—with bile, 2 or 3 drops per cubic centimeter of culture. All undissolved matter is then centrifuged out for discard and a precipitin test made on samples of the clear fluid with the 3 type serums. Three drops of the undiluted antiserum are added to about 0.7 cc. of the treated culture fluid. When incubated at 42 C. for thirty minutes and at icebox temperature over night, the antigen of any fixed type pneumococcus present is precipitated by the corresponding serum. The presence of this pneumococcus is thereby readily recognized.

AUTHORS' SUMMARY.

VIABILITY OF MYCOBACTERIUM TUBERCULOSIS IN A SEMI-ARID ENVIRONMENT. MARY HOWARD ESTILL, J. Infect. Dis. **37**:465, 1925.

Mycobacterium tuberculosis in sputum exposed to direct sunlight and in a manner to simulate as closely as possible actual community conditions is viable for longer periods of time than is generally conceded.

Guinea-pigs inoculated with sputum exposed to sunlight for 2, 3, 4, 5, 6, 12, 16, 20, 25, 30, 48 and 72 hours showed extensive tuberculous infections

AUTHOR'S SUMMARY.

STUDIES ON RESPIRATORY DISEASES. ELECTROPHORETIC POTENTIAL AND VIRULENCE OF PNEUMOCOCCI. I. S. FALK, H. GUSSIN and M. A. JACOBSON, J. Infect. Dis. **37**:481, 1925.

From measurements on 76 strains of pneumococci isolated from cases of lobar pneumonia (19 type 1; 24 type 2; 7 type 3; and 26 type 4), it appears that the electrophoretic potentials are different for the several types.

The highest potentials, aproximately 11 μ/sec, or 14 millivolts, are quite uniformly found on type 3 organisms.

The most probable sequence of decreasing potential is types 2, 1, 2, 4.

The potential on type 3 organisms is sharply marked off from the potentials on the others, generally being two or more times as high as those on organisms of the other types.

The potentials on types 1, 2 and 4 organisms are not sharply marked off one group from the other. They average approximately 5-8 μ/sec for type 1; 3.5-6.5 μ/sec for type 2; and 3-6 for type 4.

Measurements of virulence of pneumococci for white mice by the methods detailed in this paper show distinct differences for the cultures of different types. The sequence of decreasing virulence is 3, 1, 2, 4. The minimum lethal doses were found to be: type 3: 10^{-8} cc.; type 1: 10^{-7}-10^{-8} cc.; type 2: 10^{-4}-10^{-6}; type 4: 10^{-3}-0.5 cc.

The sequence of decreasing electrophoretic potential is identical with the sequence for decreasing virulence. This finding is discussed, especially in the light of anticipations that this would be found, anticipations based on the commonly observed parallelisms (direct or inverse) between virulence, agglutinability and other characteristics of bacteria and on considerations of the rôle of the electrophoretic potential in the phenomenon of agglutination.

AUTHORS' SUMMARY.

STUDIES ON RESPIRATORY DISEASES. SOME RELATIONS BETWEEN FATALITY IN LOBAR PNEUMONIA AND ELECTROPHORETIC POTENTIALS OF PNEUMOCOCCI. I. S. FALK, M. A. JACOBSON and H. GUSSIN, J. Infect. Dis. **37**:495, 1925.

Earlier experiments have indicated that, using the technic described, the sequence of decreasing virulence of pneumococci for white mice is 3, 1, 2, 4, and that this is also the sequence for decreasing electrophoretic potential. As this is also the probable sequence of decreasing fatality rate in lobar pneumonia of man it was anticipated that strains of pneumococci isolated from fatal cases of pneumonia might show larger potentials than strains of the same type isolated from nonfatal cases. Our experimental findings reported here confirm this anticipation for pneumococci of types 2, 3 and 4 and contradict it for strains of type 1. If material becomes available for reinvestigation of these relations, it may prove possible to determine the value of potential measurements in the prognosis of lobar pneumonia.

AUTHORS' SUMMARY.

STUDIES ON RESPIRATORY DISEASES. ELETROPHORETIC POTENTIAL AND VIRULENCE OF VARIANTS OF TYPE 1 PNEUMOCOCCI. I. S. FALK, M. A. JACOBSON and H. GUSSIN, J. Infect. Dis. **37**:499, 1925.

Two variant strains of pneumococci obtained by Dr. F. G. Blake from a type 1 culture grown in the presence of homologous antiserum retain their original characteristics when grown on blood agar.

We confirm the finding of early workers that these variant strains differ in virulence for white mice from the parent strain.

Our experiments demonstrate that the electrophoretic potentials on these strains parallel their virulence, the sequence for decreasing potential as well as for decreasing virulence being strains A, B, C.

We had previously demonstrated that washing pneumococci of types 1, 2, 3 and 4 with water or with salt solution results in changes in the absolute values of their electrophoretic potentials but not in the sequence of these values among the several types. The data reported in this paper show that sequence

as well as the absolute magnitudes change when the pneumococcus variants are washed.

Our experiments suggest that electrophoretic potential is related in some fundamental manner to virulence, phagocytability, agglutinability, capsule formation and other characteristics of micro-organisms.

AUTHORS' SUMMARY.

THE PECULIAR FORMS OF INFECTION CAUSED BY THE BACILLUS OF TYPHOID FEVER. A. LANDAU and M. FEJGIN, Arch. Int. Med. **37**:32, 1926.

The existence of typhoid bacteremia and positive agglutination in high dilution, 1:400, 1:800, along with a high temperature is not always an absolute proof of typhoid fever. These conditions may be observed in typhoid infection in the liver and the gallbladder. Such typhoid infection, although in some sense similar to typhoid fever, differs from the latter in (*a*) the presence of leukocytosis with neutrophilia; (*b*) the absence of roseola, and (*c*) the absence of the changes in the lymphatic system of the alimentary tract. The leukopenia with neutropenia, one of the most characteristic symptoms of typhoid, probably does not depend on the biologic quality of the typhoid bacillus but on its secondary seat in the lymphatic system of the alimentary tract.

S. A. LEVINSON.

THE TUBERCULO-COMPLEMENT-FIXATION AND INHIBITIVE TESTS. RESULTS OBTAINED BY REPEATED TESTS IN CLINICAL NORMALS, TUBERCULOSIS CONTACTS, AND 1000 CASES. A. H. W. CAULFIELD in collaboration with W. R. HODGE, M. F. MACLENNAN, F. LARUSH, W. E. OGDEN, H. MACINTYRE, G. C. ANGLIN and C. COHEN, Am. Rev. Tuberc. **11**:508, 1925.

In a group of 265 patients with a "positive parenchymatous lesion" 76.9 per cent. gave a positive complement fixation and 56.9 had a positive inhibitive reaction; of 194 "clinically non-tuberculous" patients, 53 per cent. and 11.3 per cent., respectively, reacted positively; "clinical normals" gave 59.7 per cent. and 6.4 per cent. positive reactions, respectively.

MAX PINNER.

THE BACTERIOLOGY OF SUBACUTE INFECTIVE ENDOCARDITIS. HEDLEY D. WRIGHT, J. Path. Bacteriol. **28**:541, 1925.

The author attempts to solve the question whether sterile cultures in subacute infective endocarditis are due to faulty technic. He employed various types of medium, such as broth, citrate broth, trypsin broth, lactic acid broth and agar. He also made use of anaerobic methods. He found mediums that contain trypsin or sodium citrate slightly superior to those that do not. Lactic acid had no advantage. Liquid and solid mediums were equally good. He found no advantage in anaerobic methods. Any of the mediums permits the growth of organisms if they are present even in such small numbers as one or two per cubic centimeter. He believes that failure to isolate a streptococcus from the blood stream when these mediums are used indicates the absence of the organisms in the blood. A delay of five hours in inoculation of medium with infected blood does not destroy the organisms if the blood is kept at room temperature. A delay in growth in blood cultures from these cases is largely due to a prolongation of the latent period which depends on certain peculiarities of the organisms and not on inhibiting factors in the blood.

Wright believes that agonal and postmortem cultures of blood in subacute endocarditis are unreliable because of the frequency of terminal infections, often by streptococci, from sources other than the heart.

Positive blood cultures were obtained in twelve of nineteen cases of the disease. The positive cases were always positive and the negative always negative. In certain cases no organisms are circulating in the blood. In septicemic cases actively bactericidal antibodies are present in the blood. The septicemia, which is a secondary phenomenon, is due to the escape of organisms from the lesions in the valves. Bacteria are easily demonstrated in the vegetations of the septicemic cases. They may also be demonstrated in the nonsepticemic cases in which they show evidence of undergoing degeneration. In the nonsepticemic cases they appear, microscopically, to be streptococci, but this has not been demonstrated by cultural methods.

ERNEST M. HALL.

STUDIES OF THE VIRUSES OF VACCINIA AND VARIOLA. M. H. GORDON, Med. Res. Council, Special Rep. Ser. 98, 1925.

Vaccinia.—The virus of vaccinia is particulate. It is largely held up by the ordinary Berkefeld filter; but that all of it is stopped by this filter is improbable.

In the absence of mechanical injury, the most susceptible and permeable of the surfaces of the rabbit to the virus of vaccinia is the nasal mucosa. When trauma is used, however, the skin is even more susceptible to this virus than is the nasal mucosa without trauma.

When vaccinia virus gains access to the nasal mucosa, after an incubation period of from six to eight days, a condition of acute nasal catarrh develops accompanied by a mucopurulent nasal discharge, which at the onset contains the virus of vaccinia in abundance.

Immunity of substantial degree can be produced by vaccinia virus after being heated for thirty minutes to 55 C., provided that the condition of the virus as regards potency is good in the first place, and that the dose reaches a certain critical or effective strength. After subcutaneous injection either of the raw virus or of an effective dose of the heated virus, immunity can be detected after the fourth day, and rapidly increases during the next two days; by the tenth day it is substantial; by the fiftieth day it may or may not have diminished; by the hundredth day a decrease has occurred, but a certain degree of immunity may still be detected.

Provided that the dose of the heated virus is sufficient, it can produce immunity by a variety of routes, including apparently the mere application of the heated virus to the nasal mucosa. Confirmatory evidence of this capacity of the nasal mucosa to absorb antigen has been furnished by the control observation in which the application of killed *B. coli* to the mucous membrane of the nose was followed by the appearance of specific antibodies to that micro-organism in the blood. The limits of this physiologic property of the nasal mucosa and the degree to which it can be exploited for prophylactic purposes, have still to be determined.

Vaccinia virus excites the production of specific antibodies in the blood of the rabbit after the fashion of ordinary pathogenic bacteria. These antibodies include complement-fixing antibodies and agglutinins that appear to be equally specific for the viruses of vaccinia or variola. Lysin also appears to be present in antivaccinia serum.

Antivaccinia serum has been prepared from the rabbit that possesses definitely protective properties against the virus of vaccinia; 1 cc. of it protecting

against 100 M.V.D. of virus. The constituent of the serum on which this protective property depends has not yet been identified.

Within the limits defined, the specific antibodies present in antivaccinia serum serve to measure the abundance of vaccinia virus in vitro.

Variola.—Specimens of variola virus obtained from cases of the mild and severe types of smallpox, respectively, have been found when inoculated cutaneously to affect the monkey but not the rabbit.

Vaccinia appears to protect the monkey against either of these strains of variola virus better than these strains of variola protect that animal against vaccinia.

Specimens of variola virus from five outbreaks, including three of the mild and two of the severe type of smallpox, were all found to react positively with antivaccinia serum in the complement-fixation and agglutination tests. As these laboratory reactions appear to be specific for the viruses of vaccinia and variola, there is good reason to believe that they are capable of affording valuable assistance in the practical diagnosis of smallpox—especially in doubtful cases when such help is most needed.

So far no difference has been detected between the virus of the mild or alastrim type of smallpox and of the more severe type of this disease, except in regard to virulence for the monkey. No cross tests, however, have been made of the capacity of virus from alastrim to protect a monkey against virus from severe cases of smallpox, and vice versa. Nor has antivariola serum yet been prepared by which the relation of various strains of variola virus to each other and to vaccinia, respectively, can be determined.

The pronounced susceptibility of the nasal mucosa of the rabbit to the virus of vaccinia, and the acute attack of nasal catarrh that follows after an incubation period when this virus has gained access to its nasal mucosa are matters that serve to raise the question whether the main natural mode of spread of this bovine disease may not be in part by the respiratory tract rather than entirely by fortuitous cutaneous inoculation, as hitherto supposed. As it is evident that the disease which we call vaccinia is linked up to the group of influenza and acute nasal catarrh by this observation, further information is desirable on the natural distribution and mode of spread of vaccinia virus in the animal kingdom. Such an investigation can be advocated with the more confidence since we possess a triple index wherewith to identify the presence of vaccinia virus, and to estimate its abundance.

AUTHOR'S SUMMARY.

SPECIFIC INFLAMMATORY REACTIONS ACCOMPANYING IMMUNITY. E. L. OPIE, Tubercle **7**:23, 1925.

Local anaphylaxis or Arthus' phenomenon and general anaphylaxis in part are explained by the fact that whenever antigen and antibody meet within the tissue, an acute inflammation with exudation, necrosis and hyaline thrombosis of the small blood vessels ensues. This phenomenon is closely associated with the fact that in an immunized animal the reinjected antigen does not reach the blood stream as it does in a normal organism, but is fixed at the site of injection (and inflammation). This capacity of preventing the antigen from entering the blood stream is definitely limited. The significant relations of this fixating mechanism in immunized animals to bacterial reinfection and to tuberculin sensitiveness are discussed.

MAX PINNER.

HERPES ZOSTER AND VARICELLA. A. NETTER, Bull. et mém. Soc. méd. d. hôp. de Paris **49**:192, 1925.

In this communication, Netter adds further clinical evidence to that which he has published concerning the connection between herpes zoster and varicella, in brief reports of seven cases in which herpes zoster was followed in from thirteen to twenty-one days by varicella. He also reports that Urbain of the Pasteur Institute has succeeded in demonstrating the probable identity of the two diseases in several instances by complement fixation. The author states his belief that: "Herpes zoster is not merely a specific infectious disease . . . . It is more often, if not always, a manifestation of infection by varicella."

JOSEPHS.

THE PRODUCTION OF DIPHTHERIA TOXIN IN MARTIN BROTH. M. S. SCHMIDT, Ann. de l'Inst. Pasteur **39**:875, 1925.

A salt-free peptone broth prepared according to Martin's formula is found to produce a uniform toxin more rich in flocculating substance, clearer and cheaper than that obtained by other methods.

G. B. RHODES.

THE REACTION OF YERSIN'S BACILLUS ON THE PRINCIPAL HYDROCARBONS. R. PONS, Ann. de l'Inst. Pasteur **39**:884, 1925.

Sixteen strains of *B. pestis* from human infections were found to produce acid in maltose, glucose and mannite, but never in lactose or saccharose agar mediums. Acid was not formed in mannite medium by three strains until six months after isolation.

G. B. RHODES.

TRYPANOSOMIASIS AND PEST IN RODENTS. CONTRIBUTION TO THE STUDY OF MIXED INFECTIONS. E. DI MATTEI, Ann. d'ig. **35**:945, 1925.

Rats with trypanosomiasis may also be infected with *B. pestis*. The two together exercise a cumulative toxic effect, so that postmortem examination shows hemorrhagic effusions into the body cavities, congestion and hemorrhage in the internal organs. These findings present nothing characteristic by which one can recognize the double infection. Several authors have suggested a method of differential diagnosis between trypanosomiasis and pest on the basis of the type of effusion, serous in pest infections, hemorrhagic in trypanosomiasis. Di Mattei has found the opposite to be more nearly the case.

In mixed infections, the microscopic examination of the body fluids and organs may show so many trypanosomes that the pest bacilli are entirely obscured. The true diagnosis can then be established by cultures, animal inoculation, and precipitin tests, confirming the presence of the pest bacilli.

B. R. LOVETT.

THE ACTION OF ANTHRAX BACILLI ON FERTILIZED HEN'S EGGS. M. MALAGOLI, Ann. d'ig. **35**:977, 1925.

Maffucci found that embryonal tissue of chickens is not a good culture medium for pathogenic organisms. Tubercle bacilli, cholera spirilla and others, inoculated in embryos, disappeared without producing pathologic effects. The author inoculated chick embryos with antrax cultures, and examined the eggs

for viability and presence of bacilli every few days. He concludes that anthrax bacilli in the fertilized egg inhibit the growth of the embryo. The bacilli live and produce spores which remain alive more than fifty days. The embryo is but little resistant to the action of anthrax, and after death the bacilli invade its tissues.

B. R. Lovett.

The Tissue Reaction of the Guinea-Pig in Experimental Tuberculosis. W. Pagel, Beitr. z. klin. Tuberk. **61**:641, 1925.

In the processes following the infection with tubercle bacilli, proliferation is much more prevalent than necrosis. Only the primary focus is characterized by a more pronounced necrosis. Reparative and regenerative processes are frequently found. Productive foci in the lungs do not occur in primary tuberculosis. The frequent alveolar foci are probably caused by a proliferation of alveolar cells. All this shows the marked dissimilarity between pulmonary tuberculosis in man and in the guinea-pig.

Max Pinner.

Isolation of Hookworm Larvae. F. Fülleborn, Arch. f. Schiffs- u. Tropenhyg. **29**:470, 1925.

Suspected earth is placed in a cylinder the bottom of which is of agar. On heating the agar from below, the larvae burrow into the agar. The method is illustrated.

Vaginal Bacilli. R. Tateyama, Monatschr. f. Geburtsh. u. Gynäk. **71**:136, 1925.

Tateyama found in Japan large amounts of a pure culture of Döderlein's bacilli in the vagina in 90 per cent of healthy women in the first or second month of pregnancy. They decreased in numbers later. Amenorrhea not due to pregnancy has a low degree of bacteriologic purity. He believes that the high first degree of purity is one of the signs of beginning pregnancy. In differential diagnosis, it speaks also for an extra-uterine pregnancy and against adnexal tumors. In his opinion, larger numbers of vaginal bacilli testify in favor of appendicitis as against gynecologic inflammations.

The Fluid from Induced Blisters in Syphilitic Infants. M. Soldin and F. Lesser, Deutsch. med. Wchnschr. **51**:1817, 1925.

Cantharidin blisters were produced in infants, and whenever there were cutaneous manifestations of syphilis the fluid was found to contain spirochetes. Obviously, cases may occur in which such demonstration might be of conclusive diagnostic value.

The Prognostic Value of the Urochromogen Reaction in Surgical Tuberculosis. W. Grossmann, Ztschr. f. Tuberk. **43**:475, 1925.

Patients with a favorable course of the disease and with a satisfactory end-result never have a positive reaction. In severe cases the reaction may be positive at times, but it regularly turns negative before a definite improvement is noticed clinically. A permanently positive reaction sooner allows of a grave prognosis than clinical observation alone.

Max Pinner.

DEMONSTRATION OF THE VIRUS OF TSUTSUGAMUSHI DISEASE. M. NAGAYO, T. TAMIYA, A. IMAMURA, K. SATO, Y. MIYAGAWA and T. MITAMURA, Sc. Rep. Govt. Inst. Infect. Dis., Tokio **3**:37, 1924.

There is here reported in tissue sections from various lesions of the disease, stained with azur II, the finding of principally intracellular coccoid or diplococcoid bodies, the latter with the segments joined by a faintly blue stained connective substance. The numbers of these bodies increase with the development of the lesion. From the morphology of these bodies the authors deduce that the virus is akin to *Rickettsia.*

H. E. EGGERS.

STUDIES ON THE AGENT OF TSUTSUGAMUSHI DISEASE. K. ISHIWARA and N. OGATA, Sc. Rep. Govt. Inst. Infect. Dis., Tokio **3**:41, 1924.

In inoculation sites, lymph glands and spleen of fatal cases, as well as of inoculated apes, are found small spheroid bodies, which in several cases have been cultured on ascites medium. This inoculated into apes evokes a syndrome suggestive of the human disease, with the appearance of the organism in the lesions.

H. E. EGGERS.

Immunology

COMPLEMENT FIXATION WITH BILHARZIA. PART I. THE LIPOIDAL NATURE OF CERCARIAL ANTIGEN AS USED IN THE COMPLEMENT FIXATION TEST FOR MAMMALIAN BILHARZIOSIS. N. HAMILTON FAIRLEY, J. Path. & Bact. **28**:591, 1925.

The author extracted moist, freshly dissected cercarial-infested (*Schistosomum spindalis*) livers of snails (*Planorbis exustus*) in absolute alcohol for the production of antigen. The finished product contained a high percentage of alcohol (96.65), and the residue after evaporation failed to give any of the protein color reactions.

A highly antigenic extract acting in dilutions of 1:600 was prepared by extracting dried, powdered cercarial livers with absolute alcohol. This same dried material when extracted with 90, 75, 50, and 30 per cent alcohol produced potent antigens which acted efficiently in dilutions of 1:600 ranging down to 1:300 for the 30 per cent alcohol.

Extracts prepared with alcohol of the lower dilutions contain less lipoid, and therefore show less tendency to fix complement in the presence of syphilitic serums. Higher dilutions of the concentrated alcoholic extract make it possible to work outside the zone of pseudo-positive reactions to syphilitic serums and still preserve in high degree specific antigenic function.

Potent antigen could not be extracted from dried cercarial livers with dry acetone. The acetone residue, however, when extracted with absolute alcohol was highly antigenic, and the antigenic factor could be almost completely removed by repeated extraction with absolute alcohol. The saline and 50 per cent alcoholic extracts of the acetone-insoluble and alcohol-insoluble residue had no definite antigenic properties.

ERNEST M. HALL.

TUBERCULOUS GUINEA-PIGS AND DIAPLYTE TUBERCLE VACCINATION. J. S. C. DOUGLAS, J. W. EDINGTON and F. W. SIMSON, J. Path. Bact. **28**:633, 1925.

The authors vaccinated guinea-pigs with weekly doses of 0.5 cc. diaplyte tubercle vaccine of Dreyer. Its administration was commenced before, simul-

taneously with, or after, the injection of tubercle bacilli into the animals. The results which were entirely negative are in accord with those of Kettle, Schütze and Bronfenbrenner and Straub.

ERNEST M. HALL.

AUTOHEMAGGLUTINATION IN CHRONIC LEUKEMIA. H. L. ALEXANDER and LAWRENCE D. THOMPSON, J. A. M. A. **85**:1707, 1925.

True autohemagglutination was observed in a case of chronic leukemia of undetermined type.

The autohemagglutination satisfied the criteria established by Landsteiner, Yorke, and Clough and Richter, by possessing the following characteristics: (*a*) Agglutination occurred only at temperatures below body temperature. (*b*) The agglutinated cells dispersed when the temperature was raised again to body temperature. (*c*) The agglutinin acted in like manner on human cells and on cells of various animals.

The patient's symptoms at one time suggested that he had paroxysmal hemoglobinuria, although no autohemolysin could be demonstrated.

THE IMMUNOLOGICAL PROPERTIES OF ALCOHOL-SOLUBLE VEGETABLE PROTEINS. IX. THE BIOLOGICAL REACTIONS OF THE VEGETABLE PROTEINS. J. H. LEWIS and H. G. WELLS, J. Biol. Chem. **66**:37, 1925.

There is a "wheat" group and a "corn" group of vegetable prolamines, the members of which are chemically and immunologically similar.

ARTHUR LOCKE.

THE IMMUNIZING ANTIGEN OF THE PNEUMOCOCCUS. III. THE PURIFICATION OF THE WATER-SOLUBLE ANTIGEN. WILLIAM A. PERLZWEIG and CHESTER KEEFER, J. Exper. Med. **42**:747, 1925.

Actively immunizing fractions of protein nature have been isolated from broth culture filtrates of pneumococcus type I by ultrafiltration, precipitation at a definite hydrogen ion concentration, and the separation of a soluble picrate fraction. The method appears to be suitable for the initial purification of this antigen.

AUTHORS' SUMMARY.

SEROLOGICAL STUDIES ON THE BLOOD OF THE PRIMATES. K. LANDSTEINER and C. PHILIP MILLER, J. Exper. Med. **42**:841, 1925.

While the precipitin tests do not differentiate, according to the results of previous workers, between the serum proteins of man and the chimpanzee, a clear-cut differentiation between the blood cells of man and the anthropoids was obtained by means of hemagglutinins.

According to our tests on blood specimens of white persons and negroes, constant racial serologic differences in human blood, if they exist at all, are certainly smaller than the differences between the blood of man and that of the anthropoid apes.

The serologic differences between man and the lower monkeys appear to be no greater than those between the anthropoid apes and the lower monkeys. These findings confirm the opinion that the anthropoid apes do not rank in the genealogical tree between lower monkeys and man.

AUTHORS' SUMMARY.

ON THE ANTIGENIC PROPERTY OF TUBERCULOUS ORGANS. 1. (COMPLEMENT FIXATION). G. MONTEMARTINI, Boll. d. Inst. sieroterapico Milanese **4**:175, 1925.

Extracts of tuberculous organs possess antigenic properties that vary with the organ and the method of extraction. The most sensitive and reliable preparations were obtained from tuberculous lung tissue by prolonged alcoholic extraction. This antigen is as good as bacterial antigen but even so caution is advised in making a diagnosis of active tuberculosis.

E. B. PERRY.

THE SKIN REACTIVITY TO SPECIFIC ANTIGENS IN VARIOUS FORMS OF SURGICAL INFECTION. G. MONTEMARTINI, Boll. d. Inst. sieroterapico Milanese **4**:185, 1925.

With specific antigens consisting of dilute bacterial emulsions intradermal tests on persons with streptococcus or staphylococcus infections led to the conclusion that in streptococcus infections an intense or a mild reaction indicates respectively a strong or weak defense; homologous antigens give lighter reactions than herterologous and serious infections rarely affect the reaction which is constantly positive in convalescents. In staphylococcus infections, however, the intradermal reactions decrease in the convalescent, the homologous antigen has a greater effect than the heterologous, and serious infection gives immunity that is detectable by the skin test.

E. B. PERRY.

EXISTENCE OF CYTOTOXINS. X. FRIDE, Arb. a. d. Microbiol. Inst. d. Volksunterrichtskomissariats **1**:62, 1924.

Of the specific cytotoxins hitherto described, the existence of hemolysin and spermatolysin only can be demonstrated in vitro. On the introduction of numerous normal or immune serums of organ extracts, heterogenous erythrocytes, or peptone, just as with active or passive serum anaphylaxis, there follows a common group of symptoms which have been described as due to cytotoxins. These symptoms may be ascribed to alteration of the colloid dispersion of the antigen by the antibodies of the immunized animal.

H. E. EGGERS.

COMPLEMENT FIXATION WITH PLASMA. J. TOMCIK and J. VIGNATI, Čas. lék. česk. **64**:1429, 1925.

Tomcik and Vignati report on 100 cases tested with the Wassermann and Hecht reactions and with Kabelik's modification (using hirudin plasma instead of the serum). The latter method was positive in five patients with a history of syphilis and negative Wassermann reaction. The other findings were concordant, although stronger with Kabelik's plasma method. Similar results were obtained in tuberculosis. It is concluded that the plasma method is more sensitive then the classical test, without being less specific.

ON THERMOSTABILE COMPLEMENT. R. TSCHERIKOWER, Arb. a. d. Microbiol. Inst. d. Volksunterrichtskomissariats **1**:69, 1924.

A number of hemolytic serums are found in guinea-pigs which are still active after exposure to 56 C. for one-half hour. The same phenomenon is noted in 26 per cent of normal guinea-pigs. It is apparent with 50 per cent

erythrocyte suspensions, but not with 5 per cent. From the foregoing is deduced the occasional presence of thermostabile complement.

H. E. Eggers.

Nonsterile Immunity and Superinfection. A. Brussin and T. Rubinstein, Arb. a. d. Microbiol. Inst. d. Volksunterrichtskomissariats **1**:86, 1924.

Nonsterile immunity, such as appears in mice infected with arsphenamine-resistant strains of *Tryp. brucei* and later treated with usual therapeutic doses of arsphenamine, has an extraordinarily nice specificity. Immediately after the elimination of the arsphenamine a superinfection with another race of trypanosomes is readily effected. If the original race is used, the superinfection is without result, until trypanosomic antibodies are completely eliminated. Persistence of the parasites and presence of immunity do not have a causal relationship. In this sense nonsterile immunity does not exist.

H. E. Eggers.

Theory and Method of the Serologic Recognition of Syphilis. H. Sachs, Klin. Wchnschr. **4**:1630, 1925.

A long and intensive preliminary treatment of animals with lipoid-serum mixtures (Landsteiner) brings about the blood changes responsible for a positive Wassermann reaction without any use of syphilitic material. The serodiagnosis of syphilis is nevertheless specific, as the syphilis spirochetes seem most adapted to make manifest the antigenic nature of the lipoids. Other infections (frambesia, lepra, malaria, sometimes tuberculosis and endocarditis lenta) only infrequently bring about a positive Wassermann reaction.

Arthur Locke.

Comparative Investigations of the New Sachs-Klopstock-Ohashi Flocculation Reaction for Syphilis with the Wassermann and Sachs-Georgi Reaction. F. Weigmann, Klin. Wchnschr. **4**:1687, 1925.

Of 1,000 serums investigated, the correspondence between the Sachs-Klopstock reaction and the Wassermann reaction was 88.4 per cent, of the Sachs-Klopstock reaction and Sachs-Georgi reaction 92.4 per cent, and of the Sachs-Georgi reaction and Wassermann reaction 92.2 per cent.

Arthur Locke.

Serum Sickness and Tetany. R. Hofmann, Klin. Wchnschr. **4**:1810, 1925.

The incubation of serum sickness is associated with a derangement of the ionic equilibrium (alkalosis) which brings on a tetanic hyperirritabilty. This culminates in a reversal toward acidosis, during which the exanthem comes to eruption.

Arthur Locke.

The Significance of the Trypanocidal Serum Substances in the Healing of Children's Diseases. B. Leichtentritt, Klin. Wchnschr. **4**:1899, 1925.

The serum of a healthy child injected into a mouse stimulates its reticulo-endothelial system to antibody production so that it is capable of combating a trypanosome infection. If the reticulo-endothelial system is blocked, the protection is not realized. The serum of children improperly nourished or otherwise unwell, confers little or no protection.

Arthur Locke.

TRANSMISSION OF ANTITOXIC IMMUNITY INTO THE SYSTEM OF THE NEW-BORN CHILD THROUGH LACTATION. T. IKEDA, Sc. Rep. Govt. Infect. Dis., Tokio **3**:29, 1924.

Examination of the blood of a colt, new-born from an immunized horse, was found to contain only a minimal quantity of diphtheria antitoxin. Following nursing from the immune mother the antitoxic content rose markedly, hence the author deduces that the immunity is transferred by the milk rather than via the placenta. It was found impossible to transfer antitoxin in milk through gastro-intestinal absorption to animals of heterologous species.

H. E. EGGERS.

Tumors

ROENTGEN-RAY TREATMENT OF PITUITARY TUMORS. E. B. TOWNE, Arch. Neurol. & Psychiat. **15**:92, 1926.

Two types of pituitary neoplasm cause loss of visual acuity and constriction of the visual fields by pressing on the optic tracts. The less common pharyngeal pouch tumor is primarily suprasellar and usually cystic. It is not favorably influenced by roentgen-ray treatment, and remains a surgical problem. The more common anterior lobe adenoma, primarily intrasellar, enlarges and erodes the sella and later invades the cranial cavity and causes visual disturbances. This tumor is usually diagnosed without difficulty by means of the roentgenogram and the perimeter. About 20 per cent of the adenomas are cystic. Many of these tumors respond to roentgen-ray treatment with increase of visual acuity and enlargement of visual fields, even to normal. If an adenoma is not favorably influenced by the roentgen ray, one may suspect cystic degeneration which calls for surgical treatment.

AUTHOR'S SUMMARY.

DIFFUSE TUMORS OF THE MENINGES. WILLIAM BOYD, Am. J. Path. **1**:583, 1925.

Diffuse infiltration of the meninges with tumor cells, commonly known as diffuse sarcomatosis of the meninges, is in the great majority of cases a secondary condition. While the possibility of a primary meningeal origin must be admitted, this possibility is becoming open to doubt. The mechanism of the meningeal involvement is invasion of the cerebrospinal fluid with tumor cells from some focus standing in intimate relation to the fluid, such as the choroid plexus or the wall of the ventricles. A clinical diagnosis of the condition may be made from the discovery in the spinal fluid of large pale cells in considerable numbers.

AUTHOR'S SUMMARY.

EPENDYMOMAS OF THE LATERAL AND FOURTH VENTRICLES OF THE BRAIN. EDWIN F. HIRSCH and ARTHUR R. ELLIOTT, Am. J. Path. **1**:627, 1925.

Two ependymomas of the brain are reported. One, primary in the lateral ventricle, had the infiltrative qualities of a malignant tumor, while the other, in the fourth ventricle, was chiefly an expansile growth pushing aside the adjacent tissues. This difference in growth suggests that in certain ependymomas are benign while others are malignant, and that growth characteristics should be recognized in the general class of tumors arising from the ependyma.

AUTHORS' SUMMARY.

A Multinucleated Liver Cell Carcinoma. Henry S. Rowen and F. B. Mallory, Am. J. Path. **1**:677, 1925.

A report is given of a liver cell carcinoma containing many huge multinucleated tumor cells which have originated from multiple mitoses. In addition reference is made to seven other tumors of the same type, but without multinucleated cells, occurring in 6,506 consecutive necropsies. Six of the eight cancers are associated with definite cirrhosis which is of the pigment type in three. In the other three, the cirrhosis is a combination of the pigment and alcoholic types.

Judging from these examples and others in the literature, pigment cirrhosis is the type which is most commonly complicated by liver cell carcinoma.

Authors' Summary.

Recklinghausen's Disease Without Tumor Formation; Incomplete or Abortive Forms of the Disease. Fred Wise and J. J. Eller, J. A. M. A. **86**:86, 1926.

The cutanous manifestations of Recklinghausen's disease consist, in a certain group of cases described, of nothing more than widely scattered pigment spots irregularly distributed on the trunk, buttocks and thighs. They vary from a light yellow to a deep brown, and from pinhead sized freckles to extensive areas large enough to cover a buttock or a thigh or a large area of the trunk.

This tumorless variety of the affection is usually encountered in one or more children of a family in which either parent has a typical neurofibromatosis cutis, as originally described by Recklinghausen. However, a pigmentary eruption without tumors may also occur in adults.

To this variety of Recklinghausen's disease the terms "incomplete" and "abortive" have been applied, suggesting the assumption that as the disease progresses, tumors eventually will make their appearance.

The term neurofibromatosis cutis or fibroma molluscum multiplex is applicable only to those cases in which tumors form a part of the clinical picture.

Authors' Summary.

Perforating Ovarian Cysts (Sampson's) with Invasion of the Bladder Wall: Report of Two Cases. Floyd E. Keene, Am. J. Obst. & Gynec. **10**:619, 1925.

Keene describes two cases of endometrial (Sampson's) cysts of the ovary which secondarily invaded the bladder wall and produced a cystoscopic picture sufficiently characteristic to permit a preoperative diagnosis. In the first case the chief complaint was periodic bladder pain which occurred only immediately after menstruation. In the second case there was no relationship between menstruation and the degree of bladder symptoms. The tumors were not removed, but excised bits revealed typical endometrial glandular spaces surrounded by endometrial stroma. Relief of the symptoms and restoration of the bladder to normal followed the removal of both ovaries, showing, in the opinion of the author, that excision of the bladder was unnecessary.

E. S. Gais

ADENOMA OF ENDOMETRIAL ORIGIN IN THE LAPARATOMY SCARS FOLLOWING INCISION OF THE PREGNANT UTERUS. N. SPROAT HEANEY, Am. J. Obst. & Gynec. **10**:625, 1925.

Seven cases had been previously reported in which adenomas of endometrial origin have occurred in the laparatomy scar following incision into the pregnant uterus, and Heaney describes two additional cases of his own. In one case following a high classical cesarian section and in the other following an operation for retroversion in which the cornua were excised and a six to seven weeks' ovum was removed through a fundus incision, a nodule appeared in each laparatomy scar. This became tender and enlarged during and following menstruation. Microscopically, the diagnosis was adenoma containing endometrium which in the second case was actively "menstruating." No smooth muscle was found. It is the belief of the author that pieces of the endometrium were carried to the abdominal incision, there became engrafted and produced adenomas.

E. S. GAIS.

ADENOMYOMA OF THE ABDOMINAL WALL. W. C. DANFORTH, Am. J. Obst. & Gynec. **10**:630, 1925.

Two years after cesarean section with excision of the uterine ends of the tubes there developed a hard rounded mass in the lower third of the laparotomy scar. It was tender and fixed but did not vary in size at the menstrual periods. Several spaces lined by epithelium of typical endometrial character were found microscopically. The character of the stroma is not discussed. The author thought that operative contact with the exposed endometrium or the cut ends of the tubes occasioned such implants.

E. S. GAIS.

HETEROTOPIC OR MISPLACED ENDOMETRIAL TISSUE. JOHN A. SAMPSON, Am. J. Obst. & Gynec. **10**:649, 1925.

Sampson reviews his work and divides misplaced endometrial or müllerian tissue into five groups according to the manner in which this tissue reached its ectopic situation.

1. Direct or primary endometriosis (müllerianosis) arising from direct invasion of the myometrium by the mucosa lining the uterine cavity.
2. Peritoneal or implantation endometriosis.
3. Transplantation endometriosis.
4. Metastatic endometriosis through the lymphatics or veins.
5. Developmentally misplaced endometrial tissue. This he admits as a possibility.

He concludes that the invasion and dissemination of benign endometrial tissue employ the same channels for dissemination as cancer.

E. S. GAIS.

TUMOR OF THE SMALL INTESTINE WITH SPECIAL REFERENCE TO LYMPHOID CELL TUMORS. J. HENG LIU, Arch. Surg. **11**:602, 1925.

This is a study of twelve cases of submucous lymphoid cell tumor of the wall of the large and small intestine. The lymphoid tumors occurring in the small and large intestine are the same, the essential features of which are an infiltrative neoplasm composed of round cells, somewhat larger than the

lymphoid cell, with variations in size and shape dependent on the rate of growth. The nuclei are large and vesicular and usually contain one nucleolus. Large polynucleated cells are sometimes present. Mitoses are common, and the stroma is a fine connective tissue and invasive. In these tumors the mucous membrane quickly becomes necrotic, desquamates, and an ulcer is developed at this site. In none of his series was the serosa invaded, although the muscularis sometimes was. These tumors are twice as common in males as in females and quite frequent in the first decade. The most frequent location is in the ileum and ileocecal region, and they are sometimes multiple. The gross appearance may be annular or polypoid. Some of the tumors were malignant, others benign, and no difference could be made out between those which recurred or resulted in death and those of apparently benign character. It is important to differentiate between these and carcinoma, for the latter is less frequent, usually annular, single, and infiltrates early.

N. Enzer.

The Relation of the Bone Marrow to the Lymphatic System. Its Rôle in the Spreading of Carcinomatous Metastases Throughout the Skeleton. A. Kolodny, Arch. Surg. **11**:690, 1925.

The regional lymph nodes to the upper and lower extremities of the dog were found to contain particles of India ink previously injected into the bone marrow, from which he concludes that the bone marrow possesses a lymphatic system. The occurrence of metastases to bone he considers to be through the lymphatics by retrograde flow.

N. Enzer.

No Immunity Produced by Inoculating Irradiated Tumor Tissue. F. C. Wood and R. E. Prigosen, J. Cancer Res. **9**:287, 1925.

Data from about 6,000 experimental inoculations and more than 30,000 control stock inoculations, furnish considerable evidence against the assumptions that either immunity to inoculation or resistance to a growing mouse or rat tumor can be induced by the inoculation of irradiated tumor material. If no such immunity can be produced in animals, the authors state, the experimentation on human beings should be abandoned immediately as not only useless but also as dangerous and wholly unjustifiable from a scientific point of view.

Effect of Single Injection of Irradiated Sarcoma Cells on Growth of Established Homologous Tumor Grafts. Effect of Multiple Injections of Irradiated Sarcoma Cells on Growth of Established Homologous Tumor Grafts. J. C. Small, M. J. Evans and E. B. Krumbhaar, J. Cancer Res. **9**:316 and 323, 1925.

The growth of established tumors (rat sarcoma 10) was not affected by a single injection of homologous tumor cells devitalized by roentgen-ray irradiation under the conditions of the experiments made by Small, Evans and Krumbhaar. They are convinced that the success of this method in other hands emphasizes the need for repeating the experiments with large numbers of animals and with other types of experimental tumors.

The growth of established tumor grafts of rat sarcoma 10 was not affected by three injections at weekly intervals of homologous tumor cells devitalized by roentgen-ray irradiation under the conditions of the authors' experiments.

The hypothetic biphasic action of antigens of this type requires further investigation in that it might have a bearing on the interpretation of failure to establish some degree of immunity in animals following the injection of devitalized tumor cells.

LEUKEMIA, PSEUDOLEUKEMIA AND RELATED CONDITIONS IN SLYE STOCK OF MICE. J. P. SIMONDS, J. Cancer Res. **9**:329, 1925.

Among the 316 mice in the first 15,000 necropsies of the Slye stock studied by Simonds because they showed enlargements of the lymph glands and spleen, there were found sixty-seven leukemias, of which twenty-eight were of the lymphatic, and thirty-nine of the myelogenous type; 111 pseudoleukemias, and fifty-one lymphosarcomas. Borderline or transition cases are numerous. A generalized lymphosarcoma may closely resemble a pseudoleukemia; a subleukemic pseudoleukemia is not easily differentiated from a true leukemia; a leukosarcoma partakes of the characteristics of both leukemia and lymphosarcoma, in some cases of pseudoleukemia, the lesion in one lymph gland or one group of glands may be so extremely invasive as to resemble a lymphosarcoma. An attempt has been made to establish criteria whereby these difficult cases may be classified correctly. Lympoid hyperplasia may be either local or generalized.

THE CARBOHYDRATE METABOLISM OF TUMORS. II. CHANGES IN THE SUGAR, LACTIC ACID, AND CO_2-COMBINING POWER OF BLOOD PASSING THROUGH A TUMOR. C. F. and G. T. CORI, J. Biol. Chem. **65**:397, 1925.

The sugar and lactic acid content and the carbon dioxide combining power of blood plasma drawn from the right and left wing veins of normal chickens are identical. The blood, after passing through a tumor grown on one wing, contains 23 mg. less of sugar and 16.2 mg. more of lactic acid than the blood that has passed through the tissues of the contrasted normal wing. The blood plasma from the tumor side shows on saturation with alveolar air 3.7 volumes per cent less of carbon dioxide than that of the normal side. The plasma of blood that has been collected under oil contains 0.7 volumes per cent less of carbon dioxide than that of the normal side.

ARTHUR LOCKE.

IMMUNOLOGY AND MALIGNANT DISEASE. A. EASTWOOD, J. Hyg. **24**:255, 1925.

This is a theoretic discussion of whether a stimulus to the production of nonviable variants may be regarded as of immunologic interest in relation to the therapeutic problem of cancer. "The type of transmissible stimulant which has been termed bacteriophage is not a living virus but consists entirely of material derived from the bacterial cells. . . The stimulant to malignant growth, in animals, is derived entirely from the animal cells of the host."

ARTHUR LOCKE.

CARCINOMA OF THE VERMIFORM APPENDIX. ERNEST H. SHAW, Brit. J. Surg. **13**:130, 1925.

Shaw discusses the histology of the primary tumors of the appendix and concludes that they are derived from deep-seated epithelial cells which have been cut off at an early period of fetal life. This conclusion is based on purely

morphologic considerations. No reference is made to the literature concerning the carcinoid or argentaffine tumors of the appendix, and their differentiation from the true cylindrical cell carcinomas of this organ.

LAWRENCE JACQUES.

TUMORS OF THE TESTICLE: THE SPERMATOCYTOMA GROUP. F. GORDON BELL, Brit. J. Surg. **13**:282, 1925.

Bell concludes his study of sixty testicular tumors with an analysis of the spermocytoma group, which he considers to arise from the seminiferous cells forming the glandular system of the testis. The author is convinced of the independent existence of such a group, and bases his opinion on the following observations: (1) the presence of transitions between normal seminiferous tubules and the tumor tissue, (2) the specific characteristics of the cells of many of these tumors, (3) characteristic macroscopic features, (4) the presence in two tumors of isolated seminiferous tubules showing evidences of proliferation and infiltration, (5) the frequent combination of carcinomatous and sarcomatous features, which may be accounted for by the derivation of the secretory elements of the testis from mesothelial elements which evolve in an epithelial direction. A special subgroup of carcinosarcoma is created to embrace this type of growth. No heterologous elements were seen in the sections examined from the tumors of the spermacytoma group, but the author states that it must freely be admitted that no elaborate examination to exclude their possible existence has been attempted.

LAWRENCE JACQUES.

THE MENINGEAL TUMORS: A CRITICAL REVIEW. ROUSSY and CORNIL, Ann. d'anat. path. méd.-chir. **2**:63, 1925.

Although nothing much has been added to the gross description of the meningeal tumors since the time of Virchow, it is far otherwise as concerns their histology. At present even the question of their origin is being warmly debated. Originally it was sufficient to call them psammomas on account of their calcareous concretions. Later they were named endotheliomas from the tissue from which they were supposed to spring, and only recently Cushing has swung away from the endothelial theory and given these tumors a place of their own by calling them the meningiomas. Oberling has recently brought new light to bear on this question and comes out forcibly in favor of the ectodermic origin of these meningeal tumors. Apparently they are always inseparably connected with the dura, although they may often be shelled out from the surrounding brain tissue without even the most minute destruction of the cerebral substance. They frequently extend into the bone and produce hyperplastic changes which may be recognized roentgenographically.

Histologically, there are three main types: the neuro-epithelial with bizarre nuclei and nucleoli; the fusiform neuroglial, the most frequent type, with its whorls and resemblance to the peripheral gliomas springing from the nerves; the connective tissue (fibromatous or sarcomatous) tumors, which resemble those springing from subcutaneous tissue, and which usually arise from the dura. Calcareous granules may be found in any type. The authors conclude from an extensive study that these chalk bodies arise as buds from vessels which undergo calcareous degeneration, as intravascular projections which first become hyalinized and later calcified, or from the tumor cells which elaborate a collagenous substance that is later infiltrated with lime salts.

Recent departures which classify the meningiomas with the epitheliomas are based on the development of the cerebral membranes and the histologic character of the tumors. Instead of three membranes there are only two, the dura and two or more layers of pia. The pia is projected along the nerves, forming their sheaths. Cushing objected to the name endothelioma because these tumors arise from the pia (or its superficial layer, the arachnoid), and involve the dura secondarily. Consequently, he coined the term meningioma. According to Oberling, the leptomeninges are formed from meningoblasts arranged in an extensive syncytium extending between the nervous parenchyma and the dura. These meningoblasts originate from the neuroglia, and arise from the neural tube. Several minor reasons are given for this statement: the homology of the leptomeninges with the sheath of Schwann, the presence of melanoblasts in the pia, the variety of tumors arising from the meninges, Recklinghausen's disease and, finally, the rare but important diffuse gliomatosis of the pia.

Foussy and Cornil, therefore, concur with the opinion of Oberlin that tumors of the meninges are ectodermic in origin, although a few may arise from the dura, that is, the mesoderm.

FREEMAN.

FORMATION OF METASTASES BY INJECTION OF CULTURES OF CELLS. A. H. ROFFO, Bol. d. Inst. de med. exper. **1**:685, 1925.

Tumors developed with neoplastic cells cultivated in vitro show histologic purity and marked proliferative activity. The cells retain their neoplastic character through several generations.

B. R. LOVETT.

THE ACTION OF ROENTGEN RAYS ON THE LECITHIN CONTENT OF TUMORS. A. H. ROFFO, Bol. d. Inst. de med. exper. **1**:703, 1925.

Irradiation of tumors in rats causes a reduction of the lipoid content of the tumor. Irradiation of the animal exclusive of the tumor causes a slighter reduction with a more rapid return to normal. This may be the effect of the rays on the blood and other lecithin containing organs, with secondary effect on the tumor, or the rays may cause chemical changes of the tumor lipoids directly, through hydrolyzing activity.

B. R. LOVETT.

TUMORS AND BACILLI. T. REICHERT, Deutsch. med. Wchnschr. **51**:1306, 1925.

Reichert has made studies with the bacillus P. M. which has been isolated by Blumenthal. Rat tumors which have been produced by the simultaneous injection of this bacillus and kieselguhr were transplanted into other rats. In 40 per cent. of the animals the transplantation was successful. It was found that a second transplantation into the same animal frequently led to the development of the first transplant. Reichert proved anew that these tumors grow rapidly, that they metastasize, and that they grow destructively with infiltration. The bacillus P. M. is identical with Smith's *Bacillus tumefaciens*. Since Blumenthal succeeded in isolating a number of different strains from human malignant tumors, the author queries whether these bacilli are really the etiologic factors or whether a uniform ultravirus which lives in symbiosis with these different bacilli may not be the causative agent.

A Chemical Diagnosis of Malignant Tumors. H. J. Fuchs, Klin. Wchnschr. **4**:2350, 1925.

This is a preliminary note. The blood serum of persons with malignant tumors possesses a proteolytic ferment not present in normal blood nor in the blood of persons with benign tumors. The correspondence of laboratory diagnosis with postoperative findings is 100 per cent of a total of 145.

Arthur Locke.

Blood Sugar and Carcinoma. A. Foerster and A. Forster, Klin. Wchnschr. **4**:1540, 1925.

The blood sugar values of fasting, normal persons vary from 75 to 125 mg. per cent, rise to a peak value forty-five minutes after the ingestion of 100 Gm. of glucose, and fall to the original value after two hours. Carcinomatous persons differ only in that the sugar value falls more slowly from the forty-five minute peak and does not reach the original value at the end of two hours. Similar behavior is also exhibited in cachexia of different etiologies, in long-standing benign pylorus stenoses, in cholelithiasis, and in the aged. The source of the variation is probably a general impairment of bodily functions. Only a negative finding is of value in the diagnosis of carcinoma.

Arthur Locke.

Folliculoma of the Ovary. A. Ujma, Virchows Arch. f. path. Anat. **257**:709, 1925.

Ujma reports an epithelial tumor of the ovary of the type to which the name granulosa cell tumor was applied by von Werdt and folliculoma by Aschner. The tumor tissue formed solid cell nests, in which occurred follicle-like structures, some of which contained large cells similar to primordial ova. The author discusses the possibility of origin of such tumors from normally differentiated follicular epithelium and from misplaced embryonic germinal epithelium, apparently leaning toward the first possibility.

O. T. Schultz.

Medicolegal Pathology

Carbon Monoxide Poisoning. Charles Norris, Industrial Hyg. Bull. New York State Department of Labor **2**:1, 1925.

The author discusses various phases of carbon monoxide poisoning. A saturation of 60 to 70 per cent. of the red blood cells with carbon monoxide causes death, according to the unanimous opinion of observers. The after-effects of exposure to carbon monoxide are regarded as due to asphyxia during the intoxication. These effects include thromboses and hemorrhages in the nervous system, the symmetrical areas of anemic degeneration (Kolisko) in the globus pallidus, the foci of necrosis about the distribution of the sylvian arteries. Certain deaths occurring shortly after asphyxia are ascribed to edema of the medulla and pons. Norris has seen only a few cases of so-called hemorrhagic encephalitis after carbon monoxide poisoning. In deaths due to carbon monoxide, the carbon oxide ranged from 10 to 92 per cent. In other cases carbon monoxide may be present from mere traces up to 5 per cent. (in a fireman). After death in conflagrations there may be large amounts of carbon monoxide in the blood and tissues, from 50 to 95 per cent. The VanSlyke test as modified by O'Brien and Parker is recommended by Norris not only because it is sensitive, but also because it gives a quantitative determination.

THE GROUP-SPECIFIC AGGLUTINATION OF HUMAN RED BLOOD CELLS AND ITS MEDICOLEGAL VALUE. B. LINDENBERGER, Hygiea **87**:164, 1925.

THE SIGNIFICANCE OF GROUPING OF HUMAN BLOOD IN CRIMINOLOGY. P. MORITISCH, Arch. f. Kriminol. **77**:103, 1925.

Comparison of the agglutination of red blood cells from stains supposed to be from the blood of persons accused of crime with the agglutination of the blood withdrawn from the veins of such persons and obtaining identical or unlike group-specific agglutination, has become generally recognized as a test of proved value. Similar tests may be used in efforts to determine paternity.

Moritsch describes how the tests may be made grossly without the aid of a microscope, and Lindenberger, in addition to discussing the details mentioned, considers the influence race exerts on agglutination, and the differences he found in the blood of negroes, Arabs, the Indo-European races and Jews.

E. R. LECOUNT.

A SUMMARY OF THE RESULTS OF AUTOPSIES HELD AT THE CALCUTTA POLICE MORGUE DURING 1923-1924 ON CASES OF SUDDEN DEATH. C. A. GODSON, Indian M. Gaz. **60**:469, 1925.

The contents are indicated by the title.

THE POSTMORTEM FORMATION OF GAS IN THE HEART. L. JANKOVICH, Deutsch. Ztschr. f. d. ges. gerichtl. Med. **6**:379, 1925.

Under climatic conditions such as those that prevail at Budapest, necropsies must be made within two days after death if questions of air embolism are to be answered. Jankovich determined this by filling the pericardium with water after removing the caudad part of the sternum and then watching for gas in the water when the blood escaped from the ventricles opened under water. This he did from two to twelve days after death, using 110 bodies, all without injury during life.

He frankly admits the difficulties in attributing death to air embolism caused by earlier formation of gas after death in bodies of persons who die with open wounds, deaths from gas gangrene and malignant edema and the production of gas during the period when death is occurring or postmortem by such bacteria as the gas bacillus. No mention is made of examination of the gas.

He found some gas that he believed due to postmortem decomposition in 13 per cent of bodies which grossly had not undergone any such change, and no gas at all in 12 per cent of bodies definitely altered by such decomposition.

E. R. LECOUNT.

Technical

MICROTEST FOR BLOOD SUGAR. N. JOHANNSEN, Hygiea **87**:785, 1925.

Johannsen extols the ease, simplicity and rapidity of the Becher-Herrmann technic. The findings with it paralleled astonishingly those of the more complicated methods in his extensive experience with it. It is based on the Jaffé picric acid creatinin test. The blood (0.10 cc.) is placed in the first of a set of six tubes, containing 1.9 cc. of distilled water, and then 1.5 cc. of a 1.2 per cent solution of picric acid is added. After mixing, the fluid is decanted through a filter into a graduated test tube to the line for 2.1 cc.

Then 0.3 cc. of a 4 per cent solution of sodium hydroxide is added, bringing the fluid to the 2.4 cc. mark, and it is boiled for from one to one and a half minutes, filling with distilled water to maintain it at the 2.4 cc. mark. The fluid is filtered anew into another test tube of the same caliber. The color of the fluid then, if it contains 0.10 per cent of sugar, is identical with that of a 0.25 per cent solution of potassium bichromate. The reagents keep well.

QUANTITATIVE ESTIMATION OF MINUTE AMOUNTS OF UREA. J. T. WEARN and A. N. RICHARDS, J. Biol. Chem. **66**:275, 1925.

A colorimetric method is described for the estimation of as little as 0.0005 mg. of nitrogen in the form of ammonia or urea. The probable error is within 10 per cent.

ARTHUR LOCKE.

CHEMICAL ANALYSIS OF SWEAT. ROBERT E. BARNEY, J. A. M. A. **85**:1373, 1925.

Sweat was obtained from persons in a sweat bath after injection of 0.01 gm. of pilocarpin, and analyzed according to the Folin-Wu methods for blood analysis. The amounts of nonprotein nitrogen and urea nitrogen varied within rather wide limits. There was found an apparent diminution in the output of nitrogenous elements in the sweat in senile eczema. Disturbance of salt metabolism may be expressed in the sweat as well as in the urine in chronic nephritis.

A COMPARATIVE STUDY OF THE VALUE OF STAINED SMEARS AND CULTURES IN THE DIAGNOSIS OF GONORRHEAL VULVO-VAGINITIS. SARA A. SCUDDER, J. Urol. **14**:429, 1925.

The diagnosis in cases of vulvovaginitis should depend on smears and cultures from the urethra, vulva, vaginal introitus; upper vagina and cervix. Smears are best when made with sterile slender cotton swabs which are evenly rolled, not rubbed, over sterile glass slides.

Staining should be controlled by the use of known gram-positive and gram-negative organisms such as staphylococci and *B. coli*. The alkaline modification of Gram's stain can be so standardized as to give consistent results, if standard commercial dyes and acetone are used, if the gram-positive organisms used as controls are young and actively growing, and if the work is done by trained persons.

Persistent extracellular, gram-negative, biscuit-shaped diplococci, in freshly made and carefully stained films from the genito-urinary tract of children, are presumptive evidence of gonococcal infection, even in the absence of confirmatory clinical and cultural findings. The presence of the gonococcus in the genito-urinary tract of children is not always attended by positive clinical signs; nor is there always a predominance of pus cells in those secretions which contain gonococci. Epithelial cells frequently harbor the organisms.

Negative smears, covering a period of weeks or months with negative clinical signs, are consistent with latency, and are not, necessarily, proof of cure.

The modified Thalmann medium as described by Torrey and Buckell appears to be the best differential medium yet devised for the isolation and maintenance of gonococci, both for uniform character of growth and for longevity of young as well as old strains.

Normal ascitic fluid, added to the medium at a temperature of 50 to 60 C., should be the standard type of enrichment, because it appears to be more

constant than other serous fluids, both in reaction and in growth stimulating quality. Semisolid hormone medium, reaction p_H 6.7 to 6.9, to which ascitic fluid has been added for enrichment, gives the most uniform results in maintenance of stock strains for periods of four weeks or more.

The fermentation test is at present the only means whereby the gonococcus can be differentiated from other gram-negative diplococci. The gonococcus isolated from infant cases ferments dextrose only, and, in this respect, does not differ from the adult strains.

The possibility of an overgrowth of the gonococcus in plates, by other types of diplococci (gram-positive in our experience) should be ruled out before a case of vulvovaginitis is classed as nonsyphilitic. In thirty cases of gonorrheal vulvovaginitis, no gram-negative diplococcus was found which could be confused with the gonococcus, either morphologically or culturally. In eighteen negative cases, used as controls, no organism was found which could be classed as *Micrococcus catarrhalis*.

The smear is still the most reliable criterion of gonorrheal infection, but cultural results will be consistently positive if the material is obtained during the acute stage of the disease.

AUTHOR'S SUMMARY.

COLORIMETRIC MICRO-METHODS OF BLOOD EXAMINATION. E. BECHER and E. HERRMANN, München. méd. Wchnschr. **72**:1601, 1925.

Directions are given for the quantitative determination of uric acid cholesterol, amino-acid nitrogen and indican. A qualitative test for bilirubin is described. The blood sample, 0.1 to 0.2 cc., is withdrawn from the finger into a capillary U-tube, in which it may be centrifugated after clotting. The separation of serum from cells is made by breaking the capillary tube at the interphase. Micropipets and the Autenrieth colorimeter are used. Good agreement is shown with the results obtained by established macromethods.

ARTHUR LOCKE.

BIOLOGICAL STAINS: A HANDBOOK ON THE NATURE AND USES OF THE DYES EMPLOYED IN THE BIOLOGICAL LABORATORY. BY H. J. CONN, NEW YORK AGRICULTURAL EXPERIMENT STATION, CHAIRMAN, COMMISSION ON STANDARDIZATION OF BIOLOGICAL STAINS. PREPARED WITH THE COLLABORATION OF J. A. AMBLER, S. I. KORNHAUSER, F. B. MALLORY AND L. W. SHARP, MEMBERS OF THE EXECUTIVE COMMITTEE OF THE COMMISSION. PUBLISHED BY THE COMMISSION, GENEVA, N. Y., 1925. CLOTH. PP. 151.

The purpose of this volume is summarized as follows in the preface: "The chief object of the book is to present in logical form the information which has been accumulating in the hands of the commission since it was organized. It is neither a treatise on dye chemistry nor one on microscopy; although it contains information in both fields. It is an effort to present in a form acceptable to biologists the principles of dye chemistry so far as they have a bearing on biological stains; and to discuss the suitability of the different dyes for various biological purposes, presenting data partly original and partly drawn from the literature."

It contains brief discussions of the history of biologic staining, of the general nature of dyes and their classification, of the spectrophotometric analysis of dyes, and of the theory of staining. The greater part of the volume is devoted to a presentation of the structure, as far as is known, and of the uses of the more important biologic stains. In appendixes are contained:

(1) tables of nomenclature and synonomy, including color index numbers and Schultz numbers, (2) tables of the principal uses of stains, (3) a list of biologic stains grouped by their uses, (4) the commission specifications of certain stains — as far as these have been prepared, and (5) bibliography.

The work affords much valuable information in compact and readily accessible form, and should be invaluable to any worker in biologic fields who wishes to utilize any other than routine staining methods.

H. E. Eggers.

The Clinical Value of the van den Bergh Reaction for Bilirubin in Blood, with Notes on Improvements in Its Technique. J. W. McNee and Chester S. Keefer, Brit. M. J. **2**:52, 1925.

1. The van den Bergh reaction is the best method so far available for the clinical investigation of the bilirubin content of blood serum or plasma. It has numerous advantages over other tests which have subsequently been proposed: (*a*) its extreme delicacy; (*b*) it is not given by other yellow substances which may color the plasma; (*c*) it gives important qualitative distinctions between certain forms of icterus; (*d*) it can now be used for a satisfactory quantitative estimation of bilirubin.

2. The qualitative reaction may enable a positive diagnosis of obstructive or of hemolytic icterus to be made. Pernicious anemia, except in the stage of rapid temporary improvement, can be distinguished from secondary anemias. In some diseases (for example, catarrhal jaundice, subacute liver atrophy, cardiac failure) the reaction may pass through all the stages from completely delayed to prompt direct, as the disease progresses. As a rule, however, in the commonest type of jaundice (the toxic and infective hepatic group) no information of any diagnostic or prognostic value is given to the clinician.

3. The test is of great practical value for the detection of "latent" jaundice.

4. Various alterations in the original technic have improved and simplified its use in clinical medicine.

Authors' Summary.

A New Method for Concentration of Bacilli in Tuberculous Milk. S. R. Douglas and L. J. Meanwell, Brit. Exper. Path. **6**:203, 1925.

A method of concentration is described by which the microscopic examination of milk for tubercle bacilli is made more reliable. Briefly, the method consists in shaking the milk with oil before the addition of the fat solvent (ether). Practically all the bacilli suspended in the fluid are collected in the zone between the oily and watery layers. Of thirty samples of tuberculous milk, twenty-six were positive microscopically by this method, while by the routine method tubercle bacilli were demonstrated only ten times.

The Diazo Reactions. G. Piotrowski, Arch. de mal. de l'appar. digest. **15**:798, 1925.

The bilirubin in mechanical jaundice is identical with that in hemolytic jaundice. The direct diazo reaction depends on the presence of free bilirubin in the serum; the indirect, on association of bilirubin with the proteins of the plasma. The intensity of adsorption phenomena is connected with the amount of proteins and cholesterol in the blood. Doubt is expressed as to the diagnostic value of the diazo reaction in dubious cases.

THE BEHAVIOR OF THE BLOOD SERUMS OF VARIOUS ANIMAL SPECIES IN THE BENZOIN COLLOIDAL REACTION. G. ROI, Sperimentale **79**:885, 1925.

The serum of each species has its own constant flocculation curve with colloidal benzoin.

THE DIAGNOSIS OF CARCINOMA FROM THE BLOOD SERUM, ESPECIALLY AN EXAMINATION OF THE METHOD INTRODUCED BY WIGAND. O. BOTT, München. med. Wchnschr. **72**:1959, 1925.

The tannic acid precipitation method of Wigand does not serve to differentiate the blood serum of normal persons from that of persons with incipient carcinoma. Precipitation may be secured in the higher dilutions only in instances of extensive carcinoma and of late pregnancy.

ARTHUR LOCKE.

THE SIGNIFICANCE OF THE QUANTITATIVE DETERMINATION OF UROBILIN IN THE DIAGNOSIS OF CIRRHOSIS HEPATIS. A. LICHENSTEIN, München. med. Wchnschr. **72**:1962, 1925.

In spite of the marked urobilinuria in cirrhosis of the liver, the total amount of urobilin excreted in the urine and feces does not exceed the maximum normal elimination. However, the quotient of urine-urobilin divided by feces-urobilin is greater than in other diseases associated with urobilinuria.

ARTHUR LOCKE.

LIVER FUNCTION TESTS. F. FISCHLER, München. med. Wchnschr. **72**:1970, 1925.

Fischler pleads for routine examination of urine for urobilin because it will reveal disease of the liver just as tests for albumin reveal disease of the kidney.

STANDARDIZATION OF HEMOGLOBINOMETERS BY THE REFRACTOMETER. H. C. GRAM, Acta med. Scandinav. **63**:1, 1925.

The refractometric method is suitable for standardizing and checking clinical hemoglobinometers.

INVESTIGATIONS INTO BENIGN GLYCOSURIA AND DIABETES MELLITUS. J. E. HOLST, Acta med. Scandinav. **63**:47, 1925.

Older function tests for glycosuria fail to distinguish between nondiabetic glycosuria and incipient diabetes mellitis, and a blood sugar examination should be made in every case of glycosuria not purely transitory. Patients with glycosuria with normal fasting blood sugar all run a benign course and consequently determination of the fasting blood sugar is sufficient for diagnosis and prognosis.

SIMPLE BLOOD COAGULOMETER. R. A. PETERSON, China M. J. **34**:1026, 1925.

A wide mouthed bottle is fitted with a perforated rubber stopper, two platinum wires on rods and a thermometer. Each platinum wire should be bent so that it carries four 3 mm. loops. The bottle is filled half full with water at 100 F. The platinum loops are filled with blood from a stab in the ear in rapid succession, and three minutes later the first loop on one rod is submerged. If fibrin has not formed, the blood will be laked. Successive loops are submerged at half minute intervals until one is found that remains occluded by fibrin and thus shows that coagulation is complete.

Society Transactions

MINNESOTA PATHOLOGICAL SOCIETY

The University of Minnesota Medical School, Institute of Anatomy

Nov. 17, 1925

AN ATYPICAL CASE OF PERNICIOUS ANEMIA. HENRY L. ULRICH.

History.—This case is reported because of difficulties in diagnosis and because of the unusual blood picture which developed following splenectomy.

A woman, aged 44, entered the Minneapolis General Hospital, Feb. 27, 1922, complaining of symptoms of profound anemia. In detail there was (*a*) general malaise; (*b*) diarrhea; (*c*) headaches; (*d*) loss of weight — 47 pounds (21.3 Kg.) in one year; (*e*) numbness in the legs, paresthesia of the hands, pain under the shoulder blades, short stabbing pain in the right elbow, left knee and left side of neck; (*f*) great nervousness; (*g*) polydipsia; (*h*) sinking spells and unconsciousness; (*i*) shortness of breath and precordial pain on exertion.

She had had typhoid at the age of 20 and influenza at 41. There was a history of frequent sore mouth and sore tongue; hemoptysis ten years ago, a cupful of dark blood (questionable); palpitation, shortness of breath, precordial pain and dizzy spells on exertion for ten years. She had had diarrhea the previous summer. Her appetite was good. She had had ptyalism with epigastric pain for fifteen years. She had had nocturia since childhood, frequency in the day time, dysuria at times, and lumbar pain for ten years. She had noticed that her skin was yellowish and dry during the past year. Menstruation began at 14 and was always regular; it had been irregular since last summer (1921). She had been married twenty-six years; she had eight children living and well and had had one miscarriage (the third child). Her husband was living and well. Her family history was negative.

Physical Examination.—There was a lemon tint to the skin. The mucous membrane was pale. She had had persistent glossitis for three weeks. There was some atrophy of the papillae. Tenderness was noted over the sternum. The lungs and heart were normal. The thyroid was enlarged and smooth. The abdomen was enlarged; the liver extended 7 cm. below the costal border in the mammary line; the edge was fairly sharp and hard; the surface was smooth. The spleen extended 5 cm. below the costal border. It was hard and firm. The spleen varied in distance below the costal border at various examinations.

The patient was hyperesthetic to touch, had increased tendon and muscle pain and impaired vibration(?) over the lower extremities. The reflexes were active and equal. The gynecologic examination was practically negative.

Roentgen-ray examination showed normal lungs. The gastro-intestinal tract showed hypotonus of the stomach and colon. The electrocardiogram was negative. Blood pressure was normal. The basal metabolic rate was + 16 in March. The blood serum and spinal fluid were negative for syphilis. Gastric analysis showed an absence of free hydrochloric acid. The duodenal content of biliary pigments on March 17 and on April 13 was normal. Blood examination revealed: hemoglobin, 50 to 60 per cent; erythrocytes, 3,000,000 to 3,500,000; leukocytes, 2,400 to 7,000 — usually about 4,000; no nucleated reds.

The blood picture with the enlarged spleen, all known causes for splenomegaly having been ruled out, suggested Banti's disease. The glossitis, the achlorhydria, the nervous findings suggested a case of pernicious anemia. On mature deliberation, a splenectomy was done on June 16, 1922.

The spleen was adherent to the surrounding structures and much enlarged, the weight was 520 Gm. The capsule was tense; the pulp pale red and firm, the corpuscles inconspicuous. Microscopically, the corpuscles and sinusoids were normal in appearance. There was a little increase of connective tissue in the pulp cords, but no conspicuous fibrosis. The enlargement seemed to be due to a simple hyperplasia of the pulp.

The patient made an uneventful recovery from the operation. Immediately after the splenectomy a marked leukocytosis developed, and large numbers of nucleated red cells appeared. These characteristics of the blood picture have persisted. Thirty-two examinations have been made during the three and one-half years since the splenectomy. The leukocytes have varied from 8,000 to 23,000, with an average near 14,000. The last count was 16,000. Nucleated red cells have varied from 2,000 to 30,000, seldom being below 6,000; the last count was 11,300. The hemoglobin increased slightly after the splenectomy and has varied from 30 to 60 per cent since. During the past year (1925) it has been low, from 30 to 35 per cent. The erythrocytes were usually between 3,000,000 and 4,000,000; the last count was 2,800,000. On discharge there was marked anisocytosis and poikilocytosis, which was not present at first. The patient was discharged in July, 1922.

Second Admission.—She reported at the hospital again on March 20, 1924, complaining of severe menorrhagia in addition to the symptoms present on her first admission. She tired easily on exertion.

The physical findings were: a brownish pigmentation over the body, extremities and face; mild general adenopathy; blood pressure, normal; tenderness over the sternum, clavicle and tibia. The tongue showed marked papillary atrophy. The lungs and heart were normal. The liver was 7.5 cm. below the costal border. There was some atrophy of the muscles of the hand. The reflexes were hyperactive.

Radium was inserted on April 24. On June 11, dilatation and curettement were done. On June 30, radium again was inserted. On March 25, the blood platelets numbered 200,000; on June 30, 165,000. The patient was discharged from the hospital on July 18, 1924.

Since her splenectomy and discharge from the hospital, she has been taking care of her family, including her housework. Her most recent examination, made on Nov. 17, 1925, gave the following data: pupils, equal and reacting to light and in accommodation; thyroid, full; vessels in neck full; some pulsation present. The thorax was clear on percussion. The heart area on percussion was 2 cm. by 11 cm. There was a systolic bruit in all areas and in the precordium; a to and fro murmur was heard in the neck over the jugular vein. The lungs were clear throughout the front and back. The blood pressure was 105 systolic and 60 diastolic.

The abdomen was somewhat distended over the lower half and soft throughout. The muscles were relaxed. The liver came down 7 cm. below the costal margin; the edges were fairly soft and sharp. Below the liver the right kidney was palpable. Some glands in the right groin and some in the left axilla were enlarged; none were enlarged in the epitrochlear areas. There was a small hernia above the umbilicus.

Biceps and knee reflexes were equal and active. The abdominal reflexes were active. There was some swelling about the ankles. The patient was sensitive to spinal percussion and to pin prick. On renal percussion there was pain on the left side There was some dilatation of the veins along the sacral area. The patient was sensitive to cotton and to pin prick on the thigh and lower legs. There was some stomatitis on the lower lips, gums and buccal surfaces. The throat was red; the pillars atrophied; there was some redness; the tonsils were enlarged, the uvula injected. The fundi were negative. Vibratory sense over the lower extremities was absent and present in the upper extremities.

The patient died, March 7, 1926. Necropsy revealed: the body of a well nourished person; moderate edema below the knees; left pleural cavity, 1,500 cc. cloudy fluid; right cavity, 200 cc. similar fluid; heart, 300 Gm.; no fatty metamorphosis; liver, 2,000 Gm.; moderate hemosiderosis grossly and microscopically; extensive patchy fatty metamorphosis; no hemosiderin in pancreas; abdominal aortic lymph nodes hemorrhagic in appearance, due to blood in sinusoids; cortices of kidneys very pale; bone marrow of shaft of femur red; marked hyperplasia of myeloid cells; spinal cord, no degeneration of the white columns.

This case was originally considered either Banti's disease or pernicious anemia. The final diagnosis was pernicious anemia.

A Peculiar Case of Splenomegaly with Anemia. C. J. Watson.

History.—Mrs. E. N., aged 56, was admitted to the University Hospital on May 8, 1925, complaining of dizziness, dyspnea, edema of the ankles, purpuric eruption, polyuria and weakness, all of three years' duration, and of enlargement of the abdomen of two years' duration. The purpuric eruption was most marked on the face. Red to purple blotches would appear rather suddenly on the skin, remain a few days, then disappear. These blotches occasionally bled. The patient had been unable to do any housework for the past two years. There was rather rapidly increasing enlargement of the abdomen during that period. In November, 1924, Dr. Hebeisen of Carver, Minn., advised operation for abdominal tumor. She was seen by Dr. Schaaf of Minneapolis early in 1925. He referred her to the University Hospital for further study. The past history was essentially negative. Menopause occurred three years ago, or at about the time of the onset of the present complaints. She had lost 30 pounds (13.6 Kg.) in weight since the winter of 1924. Her present weight was 110 pounds (49.9 Kg.).

Physical Examination.—The patient's skin was white, although tan to brownish yellow in places. There were pinpoint hemorrhages on the forehead and face and larger hemorrhages, some of them old, on the arms and legs. The upper teeth were artificial; the lower teeth were carious. The tonsils were definitely enlarged. The apex of the heart was 10 cm. to the left in the fifth interspace. There was a faint systolic murmur at the apex, greater in the third interspace at the left. The pulse was normal. The blood pressure was 150 systolic and 90 diastolic. The spleen was greatly enlarged, extending to the right of the midline in the umbilical region. The edge was firm, smooth and rounded, the notch palpable. The liver edge was palpable just below the costal margin. Neurologic examination was negative.

Laboratory Examination.—Urinalysis revealed: albumin, at times; leukocytes, constant; red blood cells on several occasions; specific gravity, 1.016 to 1.022;

no casts. There was no blood in the stools on repeated examinations. Examination of the gastric contents revealed: (1) fasting: total acidity, 18; free acidity, 0; (2) Ewald meal: total acidity, 76; free acidity, 18; no blood. Blood examination on admission revealed: hemoglobin, 65 per cent; red cells, 2,200,000. During the stay in the hospital the hemoglobin varied from 65 to 55 per cent and the red cells from 3,000,000 to 2,200,000. The leukocyte count varied from 1,750 to 3,300; once it was as high as 8,000. In the smears, the erythrocytes showed normal chromemia to hypercromasia with anisocytosis, poikilocytosis, polychromatophilia, normoblasts. A representative differential count of white cells was: 200 cells counted; 50 per cent polymorphonuclears, 29 per cent lymphocytes, 4 per cent monocytes, 1 per cent eosinophils, 7 per cent basophils, 8 per cent neutrophilic myelocytes.

Myelocytes seemed to occur in showers of 4 per cent to 12 per cent. The basophilia was more or less constant. Occasional stem cells were noted.

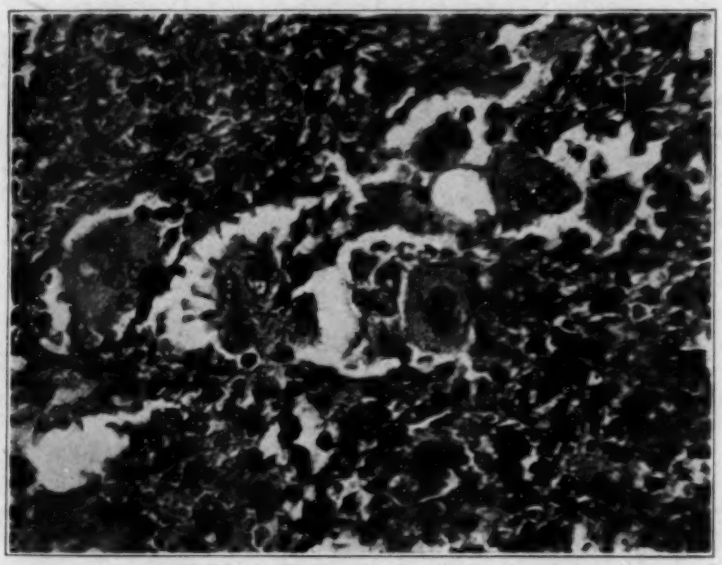

Fig. 1.—Spleen, showing megakaryocytes in the sinusoids.

Fragments of megakaryocytes and megakaryocytic nuclei with little or no cytoplasm were noted frequently. Platelets: once as low as 32,000; again 88,000; usually between 200,000 and 400,000. Bleeding and clotting times were normal. In hypotonic salt solution, hemolysis began at 0.44 per cent and was complete at 0.38 per cent.

Van den Bergh reaction on the blood serum: direct reaction, negative; indirect reaction, positive. Quantitative test, 1.45 units. Roentgen-ray examination of the chest and fluoroscopy of the bowel were negative. Pelvic examination was negative. The temperature occasionally rose to 100 and 101 F. The following diagnoses were considered: (1) myelogenous leukemia in the aleukemic phase, (2) Banti's disease, (3) pernicious anemia and (4) primary tuberculosis of the spleen.

Operation and Course.—Splenectomy was performed by Dr. A. C. Strachauer on Aug. 29, 1925. The spleen was easily delivered and removed. A small

piece of the liver was removed for microscopic study. The patient left the operating room in fairly good condition. She was discharged on Sept. 21, 1925, unimproved.

Reports from Dr. Hebeisen on November 6 and 17 indicated that the patient was becoming progressively weaker, more emaciated and more anemic. There were apparently no remissions. Death occurred on Nov. 26, 1925. Unfortunately, permission for necropsy could not be obtained. The leukocyte count by Dr. Hebeisen about one month before death was 1,700.

Pathologic Examination.—The spleen weighed 2,700 Gm. The external surface was smooth. The cut surface showed a slight diffuse fibrosis.

Microscopic examination showed that the sinuses of the spleen were somewhat prominent, although apparently diminished in number (figs. 1 and 2). There was diffuse hyperplasia of the pulp reticulum between the sinuses; in certain areas this amounted to fibrosis. The nuclei of the reticular cells were

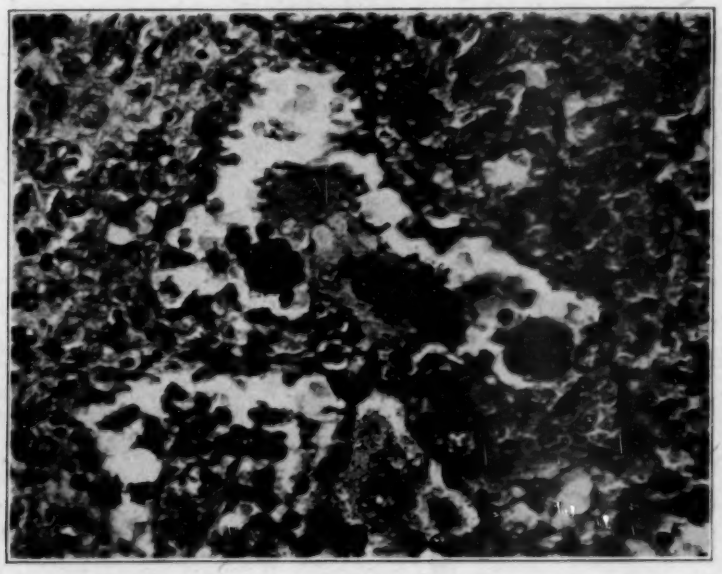

Fig. 2.—Sinusoid of spleen showing connection of megakaryocyte with the reticulum.

usually round or oval and quite vesicular. The most striking feature was the presence of large, usually multinucleate cells, occurring here and there in the sinuses and occasionally in the pulp, partially projecting into the sinuses. These cells for the most part had an abundant amount of cytoplasm, finely granular in structure and commonly forming pseudopodia. The polymorphonuclear forms were most common. The nuclei of these were almost identical with those of the hyperplastic reticulum mentioned above. Apparently many of these giant cells had pushed through the sinus wall, leaving a portion of their cytoplasm still in syncytial connection with the reticulum of the pulp. Others were noted which seemed to be definitely attached to the reticulum of the sinus wall; in addition, many were lying free in the sinuses. Some of the latter were mononuclear forms, having very large nuclei and relatively less cytoplasm. These nuclei were more darkly staining, with coarser chromatin strands.

In the liver (fig. 3) these large cells were present in even greater numbers. Here they were found in the sinusoids, without any apparent connection with the endothelium. The cytoplasm of the individual cells was usually considerable, and often much elongated, following the sinusoid. Cytoplasmic processes were frequently seen. Occasional large, dark staining nuclei, practically devoid of cytoplasm, were noted.

Sections of liver and spleen, stained with Wright's stain for tissue, using the technic described in his original article (*J. Morphol.* **21**:263, 1910-1911), showed the cytoplasm to be a hyaline blue containing many red to purplish granules, corresponding with his description of the platelet cytoplasm of the megakaryocytes.

Using Mallory's technic, sections of liver and spleen were stained for hemosiderin, and a definite increase in this substance was found in the liver cells.

This histologic picture does not correspond to that of any previously described condition, as far as we can determine. Dr. Hal Downey expressed

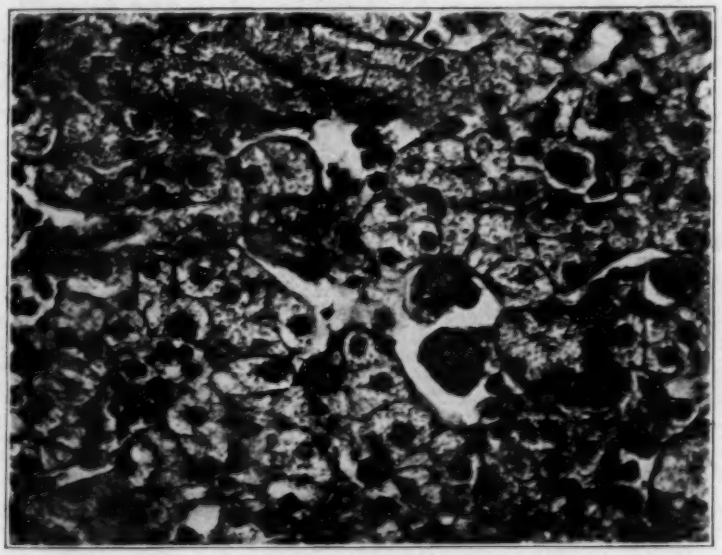

Fig. 3.—Liver, showing megakaryocytes free in the sinusoids.

the opinion that the multinucleate giant cells in both spleen and liver are megakaryocytes. Minot (*J. Exper. Med.* **36**:1, 1922) has reported forty cases in which megakaryocytes were noted in varying number in the blood stream; thirty-five of these were instances of myeloid leukemia in which the megakaryocyte count was usually from 1 to 4 per cent of the total white count, although in one case it was as high as 18 per cent. Minot points out, however, that the lung capillaries usually block the further passage of the normal megakaryocyte and that, consequently, those seen in the peripheral circulation are most commonly fragments, or simply nuclei, with little or no cytoplasm. Aschoff (*Virchows Arch. f. path. Anat.*) has shown that the lung capillaries frequently lodge the naked megakaryocyte nuclei, freed in the sinuses of the bone marrow, after their platelet cytoplasm has been completely removed. The megakaryocytes seen in the spleen and liver, described above, in nearly every instance had abundant cytoplasm. Because of this, and because connection

with the spleen reticulum could frequently be shown, it seems most likely that these megakaryocytes were formed in the spleen, and did not originate in the bone marrow. Accepting this theory, their presence may be taken to indicate a form of myeloid metaplasia.

With these facts in mind, two possible explanations demand consideration:

1. Is this a megakaryocytic leukemia? Many leukemias have been described in which only certain derivatives of the stem cell have been increased in quantity, i. e., stem cell leukemias, myelocytic leukemias, eosinophilic and basophilic leukemias and monocytic leukemias. Some writers consider that the true polycythemias may properly be classed in the leukemia group. It is not impossible, then, that this case may represent a type of leukemia in which the overproduced stem cell derivative is the megakaryocyte.

2. Is this an aplastic form of pernicious anemia in which the spleen attempted to respond by the formation of megakaryocytes? From a clinical standpoint, the purpura, the severe primary type of anemia with high color index and very little evidence of regeneration, with lack of remissions, all fit in readily with this conception. The low platelet count on admission, later rising to and maintaining a normal level, may have some significance in connection with the overproduction of megakaryocytes. The increase in hemosiderin noted in the liver is much more compatible with a pernicious type of anemia than with the ordinary leukemias, although many leukemias in their late stages are accompanied by a pernicious type of anemia. Unfortunately, the failure to obtain permission for necropsy prevented more positive conclusions.

FOLLICULAR SPLENOMEGALY BRILL'S TYPE? KANO IKEDA.

Early this year, Brill, Boehr and Rosenthal reported three cases of splenomegaly which they designated "splenomegalia lymphatica hyperplastica," a hitherto undescribed type of hyperplasia of lymph nodes and spleen, which they recognized as a disease entity.

The first case recalled by these investigators was that of a woman who presented a general adenopathy with a very large spleen and a negative blood picture. A lymph node and the spleen showed a giant hyperplasia of the malpighian bodies. About ten years later, 1923, they saw two other cases in women, aged 28 and 32, respectively, presenting a similar clinical problem, in which the examination of the lymph nodes and spleen revealed an identical histologic picture. These were reported in detail. The cardinal symptoms, such as dyspnea, cough and an increase in the size of the abdomen, were mainly referable to the generalized lymph adenopathy. The presenting symptoms were the enlarged lymph nodes of two years' duration in one, and general weakness of one year in the other. The abdominal enlargement was not noted until about two months before admission in both instances. The liver was enlarged in one and not palpable in the other.

Laboratory findings were essentially negative. In the first case, hemoglobin was 72 per cent; leukocytes 6,000 with polymorphonuclear neutrophils 71 per cent, lymphocytes 15.5 per cent and monocytes 10 per cent; platelets 160,000. In the second, hemoglobin was 95 per cent on entrance and 75 per cent a month later; leukocytes 11,000, with polymorphonuclear neutrophils 42.3 per cent, lymphocytes 49.3 per cent and monocytes 7 per cent; platelets 105,000.

The spleen was enormously enlarged, one weighing 1,800 Gm. The capsule was smooth and thin. The cut surface was thickly studded with grayish nodules, some measuring 3 mm. in diameter This was the only striking gross finding. The pulp showed some congestion. Microscopically, the average

malpighian body was three or four times larger than the large lymphoid follicles of the nodes. It was almost entirely made up of lymphoid and endothelial cells, cells with considerable cytoplasm and containing pale staining nuclei, rich in chromatin. As in the lymph nodes, these enormous malpighian bodies were surrounded by a distinct zone of lymphocytes. The pulp was congested and less cellular. The reticular tissue was increased in one and unchanged in the other.

It was contended by the authors that a hypertrophy of the malpighian bodies, such as is observed in lymphotism, low grade prolonged chronic infections, etc., had never been known to approach the degree seen in these cases of splenomegaly.

History.—Mrs. A. H., Norwegian, aged 43, married, was admitted to the Minneapolis General Hospital on July 6, 1925, complaining of a tumor in the

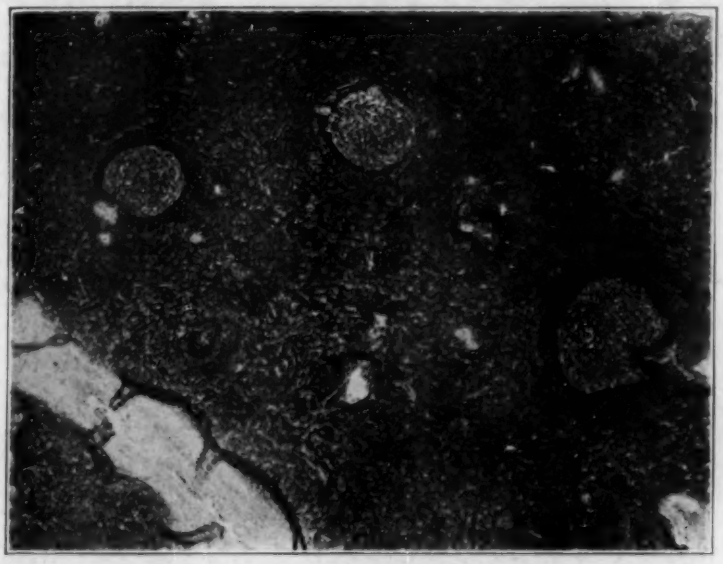

Fig. 1.—Area of spleen under low magnification showing large follicles.

left side of the abdomen, extreme weakness, headache, constipation, general body pain and pain in the region of the mass. This pain was of about three months' duration, was dull, constant and did not radiate. She had suffered from constipation for eight years, and had passed black stools occasionally since March, 1925. The abdominal mass had been present at least one month before the admission, according to the patient. She had never been very strong. An operation on the cervical glands was performed in Norway many years ago. She had an attack of acute "rheumatism" in 1915, when her knees, elbows, shoulders and fingers became swollen, red and hot, and she was confined to bed for some time. She was at a tuberculosis sanatorium for one year, 1918, at which time a positive sputum was obtained. Her menstrual history was normal; her last period occurred in 1916. She had borne five children.

Physical Examination.—Her heart was slightly enlarged. There was a systolic murmur at the apex, transmitted to the axilla. Her blood pressure

was 126 systolic and 80 diastolic. A few moist râles were heard, particularly in the base of the right lung.

The liver extended down 10 cm. below the costal margin in the nipple line and in the midaxillary line. It reached 11 cm. below the xiphoid process. The edge was not sharp or nodular.

The spleen was easily palpable in the left half of the abdomen. It extended downward vertically 13 cm. below the costal margin at a point 3 cm. from the midline to the left, 11 cm. in the nipple line and 9 cm. in the midaxillary line. The edge was fairly sharp and notched just below the costal margin 5 cm. to the left of the midline.

Some of the phalangeal joints were enlarged and partly ankylosed in a flexed position.

Nodes in the axillary and inguinal regions were only slightly enlarged. The largest was in the right inguinal region which measured about 1 cm. in diameter.

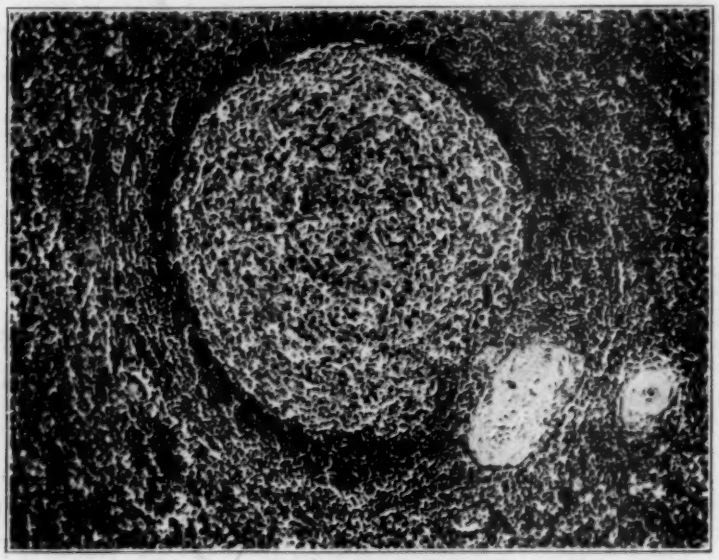

Fig. 2.—Splenic follicle, higher magnification.

The temperature and respiration were normal.

Laboratory findings were as follows: hemoglobin ranged between 65 and 75 per cent (Sahli); erythrocytes betwen 3,500,000 and 4,300,000; leukocytes between 600 and 1,200, most frequently about 900, with a differential count showing a lymphocyte percentage of from 68 to 88 per cent. These lymphocytes were of the mature type. Platelets 150,000; coagulation time, six and one-half minutes; bleeding time two and one-half minutes. The Wassermann test was negative. The fragility of the red blood cells was within the normal range. There were no bile pigments in either the plasma or the urine. The feces and the urine were normal. The spinal fluid was normal. The liver function test was normal. Neurologic examination showed the Argyll Robertson type of pupils, but no other signs of tabes. The stereoscopic roentgenograms of the chest showed chronic bronchitis or bronchiectasis in the bases, most marked

in the right. Diagnostic possibilities: Banti's disease, tuberculosis of the spleen, syphilis of the spleen, Hodgkin's disease, Gaucher's disease.

Operation and Course.—Splenectomy was done Aug. 20, 1925, one and a half months after admission.

The patient made a satisfactory recovery and was discharged from the hospital on Sept. 21, 1925, or a month following the operation.

The patient showed a temporary rise in leukocytes to 17,800 on Aug. 27, 1925, with 89 per cent polymorphonuclear neutrophils. On the day of her discharge, the blood examination showed hemoglobin, 75 per cent; erythrocytes, 4,520,000; leukocytes, 6,500, with a differential count of polymorphonuclears, 51 per cent; lymphocytes, 40 per cent, and monocytes, 7 per cent. Subsequently, Oct. 28, 1925, the hemoglobin content was 85 per cent erythrocytes, 5,130,000; leukocytes, 7,000; differential count: polymorphonuclears, 21 per cent; lymphocytes, 71 per cent; monocytes, 3 per cent; platelets, 250,000. The morphology of erythrocytes and leukocytes was normal. On Nov. 16, 1925, the hemoglobin content was 80 per cent; erythrocytes, 4,350,000; leukocytes, 5,800; differential count: polymorphonuclears, 20 per cent; lymphocytes, 60 per cent; monocytes, 13 per cent; eosinophils, 5 per cent. On this day the patient reported that she felt well. Her appetite was good, and she felt much stronger. No appreciable adenopathy was noted.

A small piece of the liver, removed at the operation, was entirely normal microscopically.

The spleen weighed 890 Gm. It was firm in consistence. The capsule was thin, smooth, tense and dark blue. On section the pulp was dark red and appeared solid and rubberlike in consistency. The trabeculae were inconspicuous. The malpighian corpuscles were uniformly enlarged and prominent. They were about 1 mm. in diameter.

Microscopically, the pulp showed a definite increase in reticulum cells. Their deep atypical staining reaction, according to Dr. Downey, would seem to indicate some toxic reaction. There was no evidence of fibrosis. The malpighian corpuscles were enlarged and made particularly conspicuous by a definite zone of lymphocytes which surrounded the germinal centers. The latter showed a marked hyperplasia of reticulum cells and contained few large and small lymphocytes and plasma cells, the enlargement of the follicles being entirely due to the reticular hyperplasia.

This case resembles those described by Brill in the prominence of the malpighian corpuscles and the absence of changes in the pulp. The chief differences are: (1) the persistent and marked leukopenia with a definite suppression of polymorphonuclear neutrophils; (2) the relatively inconspicuous lymphadenopathy; (3) the smaller size of the malpighian corpuscles (less than half the diameter of those in Brill's cases). In spite of these evident discrepancies, the case seems more nearly related to Brill's cases than to any other known form of splenomegaly.

A hyperplasia of the malpighian bodies of the spleen, showing characteristic germinal centers with a definite zone of lymphocytes, such as is present in our case as well as those of Brill, is not a common occurrence in the spleen of the adult. The character of the reticulum cell reaction, in our case, would seem to indicate a strong possibility of a low grade chronic infection (Downey). This assumption is strengthened by the persistent leukopenia with a definite suppression of granulocytes which, according to Downey and Naegeli, is an evidence of low grade infection.

The structure of the spleen is shown in figs. 1 and 2.

A Case of Darling's Histoplasmosis Originating in Minnesota. Cecil J. Watson and William A. Riley.

In a series of papers, Samuel T. Darling, 1906-1909 (*J. A. M. A.* **46**:1283, 1906; *Maryland M. J.*, April, 1907; *Arch. Int. Med.* **2**:107, 1908; *J. Exper. Med.* **11**:515, 1909) described a peculiar disease characterized clinically by splenomegaly, emaciation, irregular pyrexia, leukopenia and anemia, which he had encountered in three cases in the Ancon Hospital, Canal Zone, Panama. The patients were a Chinese, who had lived for fifteen years in the Canal Zone, and two negro laborers from Martinique.

In the endothelial cells in the smaller lymph and blood vessels and capillaries were enormous numbers of a small encapsulated micro-organism to which Darling gave the name *Histoplasma capsulatum*. Referring to this, the disease was designated *histoplasmosis*.

Since Darling's findings, no additional cases of histoplasmosis have been found, although the disease has been noted in the textbooks as a distinctively tropical disease. Bates (Ref. Handbk. M. Sc., ed. 4, **5**:280, 1923) as late as 1923 says: "Although no cases have been seen in Panama since 1906, it is probably to be found in unhygienic and less salubrious regions of tropical America not yet disturbed by the sanitarian." In view of these facts, the occurrence of a case in a woman who had lived in Minnesota for the past forty-two years is of especial interest. As shown by the history which follows, the case was typical of those described by Darling. The parasitic organisms (fig. 2) were unmistakably those of histoplasmosis.

History.—Mrs. P. M., aged 52, admitted to St. Mary's Hospital, Minneapolis, service of Dr. H. B. Sweetser, Aug. 12, 1925, was born in Germany (Rhineland). She moved to the United States when 7 years old. She was healthy and hard working until a miscarriage twelve years ago, according to the older sister. She weighed 140 pounds (63.5 Kg.) at that time; two years ago she weighed 116 pounds (52.6 Kg.). She was examined by Dr. H. C Arey, Excelsior, Minn., at the time of the miscarriage, and the abdomen was normal. Her husband said that she had had a cough for more than twenty years. Four weeks before death, the patient developed symptoms of an acute upper respiratory condition, with severe dyspnea and cyanosis in asthmatic spells of short duration. There was clinical evidence of bronchopneumonia in the left lower lobe two weeks before death. The temperature was not higher than 102 F. Seven days before death severe hemoptysis or hematemesis occurred. The leukocyte count was 3,000. The base of the left lung was still consolidated, but apparently beginning to resolve at this time.

Physical Examination.—When the patient was examined in the hospital, there was diffuse dark yellowish pigmentation of the hands and arms, extending to the elbows and less marked on the face. There were subscleral yellowish wedges on each side of the cornea, bilateral. Other findings were: edema of the ankles; mouth and skin generally cyanotic; no jaundice; bronchial breathing over the right middle and lower lobes and left apex; apparently normal heart; large, hard spleen and liver, both tender; marked ascites; temperature, 99 to 101 F.; pulse rate, 90 to 145; respirations, 30 to 40. The patient died on August 13 in apparent respiratory failure.

Laboratory Examinations.—The sputum was negative for tubercle bacilli. Urinalysis revealed: albumin, hyaline and many granular casts and occasional leukocytes. Blood count showed: hemoglobin, 85 per cent; red cells, 3,830,000; leukocytes, 4,600; differential count: polymorphonuclears, 87 per cent; small

lymphocytes, 21 per cent; monocytes, 12 per cent. Slight anisocytosis, poikilocytosis and polychromatophilia were present. There were occasional microcytes, macrocytes and normoblasts.

Necropsy.—This was performed at 10 a. m., Aug. 13, 1925. The body was that of a well developed and fairly well nourished, adult white woman; estimated weight, 105 pounds (47.6 Kg.). There were many small, pale bluish discolorations over the abdomen, edema of the legs and ankles and cyanosis of the lips and finger tips.

The peritoneal cavity contained 2,000 cc. of serous fluid. The right pleural cavity contained 1,000 cc., the left 500 cc. The heart and pericardium were normal. The lungs were more or less diffusely consolidated; crepitation was reduced throughout. There was mixed fibrosis and consolidation, most marked in the upper portion of the left lower lobe. Small amounts of pus could be expressed from this and other areas. There was a bilateral purulent bronchitis.

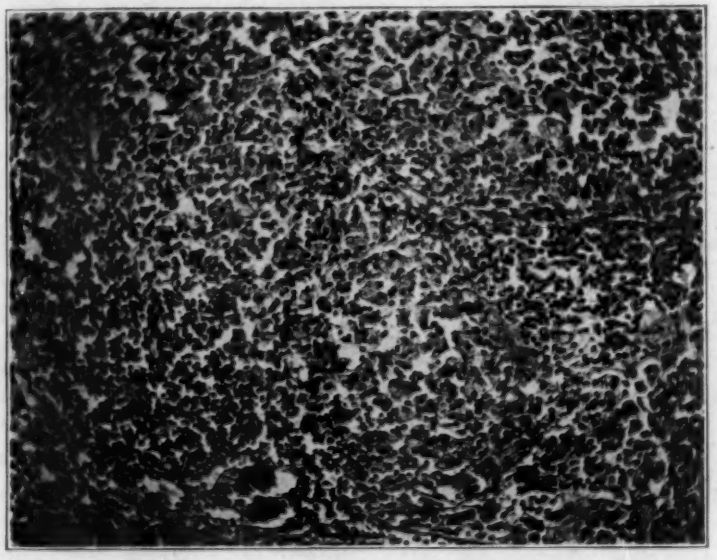

Fig. 1.—Area of consolidation in lungs. This shows general character of granulomatous type of inflammation with heavily parasitized macrophages; × 300.

The spleen weighed, 1,450 Gm. The lower pole was 12 cm. below the costal margin in the midclavicular line. On section, the organ was firm and dark red and exhibited only a slight fibrosis grossly. The liver weighed 2,250 Gm. and was 10 cm. from the costal margin in the midclavicular line. Grossly, the typical appearance of a coarse hobnail cirrhosis was presented.

There were large, firm, discrete lymph nodes, some as large as a hen's egg, along the splenic vessels, the aorta and the common iliacs.

Microscopic Changes.—The sinuses of the lymph nodes were filled with macrophages (large mononuclear cells), most of which contained many parasites (some as many as 20) (figs. 2 and 3). The lymphoid tissue between the sinuses showed numerous areas of hyaline degeneration, and there were

giant cells near some of the hyaline masses. Figure 1 shows the granulomatous areas in the lung. There were also numerous small bands and nodular masses of scar tissue containing carbon pigment and resembling healed tuberculosis. The alveoli throughout the consolidated areas were filled with macrophages resembling those in the lymph nodes and containing many parasites. There were no polymorphonuclears, and no fibrin was found. There was a dense lymphocytic infiltration in the walls of the bronchi. The spleen showed a large number of macrophages filled with parasites throughout the pulp. The corpuscles were unchanged. There was no definite increase of fibrous tissue in the pulp. The liver showed a marked lymphocytic infiltration of the portal tissues with a moderate increase of connective tissue. There were areas of hyaline degeneration in the portal tissues resembling those in the lymph nodes. There was moderate fatty metamorphosis. There were numerous small inflammatory foci containing macrophages filled with parasites. In the cortex and medulla of the suprarenals there were similar inflammatory foci. The other organs showed no definite changes.

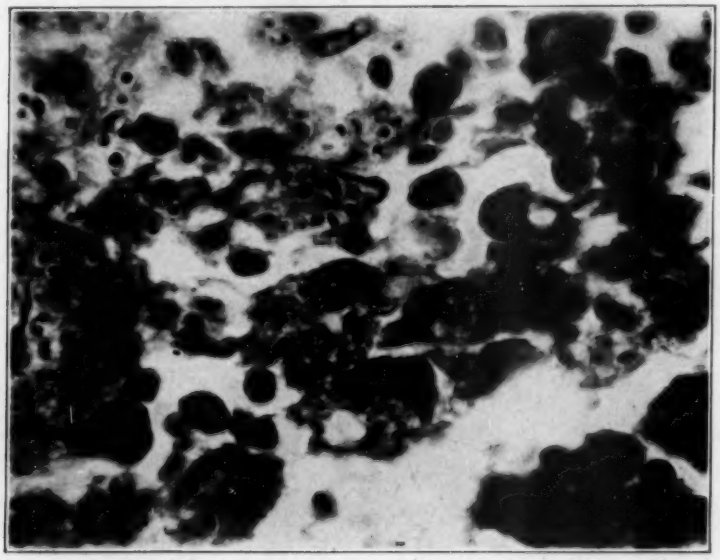

Fig. 2.—High power view of mesenteric lymph nodes to show parasites in macrophages; × 900.

The parasites were minute ovoid micro-organisms first noted in our hematoxylin stained preparations, and on account of the general syndrome and their position were suggestive of Leishman bodies. Their general appearance is well brought out in figure 2, a photograph of the heavily parasitized reticular cells of a lymph node.

On trying more special stains, such as Bensley's anilin acid fuchsin and methyl green, Giemsa's or Harris' hematoxylin with a counter stain of aurantia, they were brought out much more clearly, and it became evident that we were not dealing with the Leishman bodies. The measurements along the longer diameter, exclusive of the capsule, were from 2 to 4 microns, and thus agreed with those of the kala-azar organism However, the parasite was not binucleate, the characteristic rodlike kinatonucleus of Leishmania being absent.

The definite achromatic capsule and the staining reaction of the cytoplasm were also distinctive. We became convinced that we were dealing with *Histoplasma capsulatum* of Darling, 1906.

Darling's first case was that of a Martinique negro laborer who had died in the Ancon Hospital. At necropsy smears from a peculiarly white atypical tubercle in the lung and from the spleen, liver and bone marrow showed an intense invasion of large endothelial-like cells by small round or oval microorganisms. The report on this case (*J. A. M. A.* **46**:1283, 1906) was accompanied by crude sketches, which were little more than suggestive of the organisms which he described. In 1909, however, he presented (*J. Exper. Med.* **11**:515, 1909) a series of excellent photomicrographs which could have been duplicated from the material before us. Especially is this true of the large reticular cells of the spleen, which are greatly increased in numbers and crammed with the parasites.

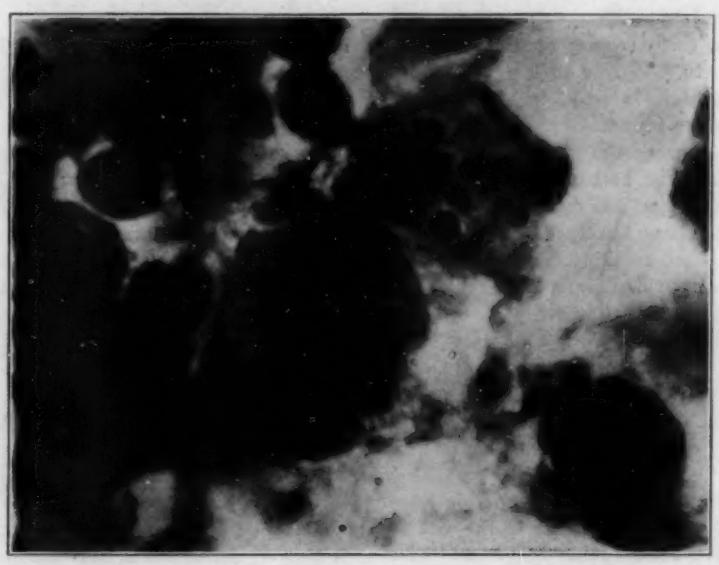

Fig. 3.—Same as figure 2; × 1800.

Darling was impressed by the fact that clinically and pathologically the disease was suggestive of kala-azar, but he recognized that the causative organism was different from the Leishman-Donovan body, "sufficiently so to warrant its being placed in a different order." For these reasons, he established for the parasite the new genus *Histoplasma*. Referring to the achromatic capsule he christened the species *capsulatum*.

Specimens of Darling's material were submitted to Major Ronald Ross who likewise regarded it as a protozoan organism, resembling somewhat the Leishman-Donovan body, but differing from it chiefly in not containing the chromatin rod usually seen in the Leishman-Donovan body.

On the other hand, Rocha Lima (*Centralbl. f. Bakteriol.* I, Orig. **67**: 233, 1912) in 1912 called attention to the close resemblance of Darling's organism to *Cryptococcus farciminosus* Rivolta 1873, the causative organism of

epizootic lymphangitis of horses and other solipeds. Contrary to a considerable group of workers who have studied Rivolta's organism, Rocha Lima regarded it as a yeast. His conclusions have been supported by subsequent studies and have been widely accepted.

We shall discuss elsewhere the question of the nature of the parasite. The important fact for us now is that *Histoplasma capsulatum* Darling, 1906, and *Cryptococcus farciminosus* Rivolta, 1873, are undoubtedly closely related, whether the latter be a protozoon or a protophyte.

Especially suggestive is the fact that there are on record at least three cases of the occurrence of epizootic lymphangitis in man contrated from affected horses.

The first of these was recorded by Brault in 1910 (Harlem, 1910; cited by Nègre and Bridré, 1911). Data regarding it are not at hand. In 1911, Nègre and Bridré (*J. Bull. Soc. path. exot., Paris* **4**:384, 1911) briefly recorded the case of a veterinarian in Algeria who, having an open wound on the thumb, operated on a horse suffering from epizootic lymphangitis.

The third case, that of Ziemann (1912, cited by Knuth and du Toit, 1921) relates to a farmer in Kamerun, who worked much with an infected horse and was himself infected in the breast. In the pus from the wound the cryptococci were found.

In view of the similarity of the organisms of histoplasmosis and epizootic lymphangitis, and of the further fact that the subject of this report had lived practically all her life on a farm, the question naturally arises as to whether she may have obtained her infection from a diseased farm animal.

Opposed to this conclusion is the fact that epizootic lymphangitis expresses itself in purulent inflammation of the superficial lymph vessels and the mucous membranes, with abscesses of the associated lymph nodes. According to Knuth and du Toit (Mense's Handbch. d. Tropenkrankh. **6**:717, 1921), the inner organs are almost without exception unchanged.

Moreover, in spite of repeated statements in the literature to the effect that the disease occurs in horses in several states, including North Dakota, the studies of Page, Frothingham and Paige (*J. M. Res.* **23**:137) and of Meyer (*Am. J. Trop. Med.* **3**:144, 1915) seem to have demonstrated definitely that the disease so diagnosed in this country is in reality a sporotrichosis. This, of course, does not preclude the possibility of the equine disease occurring, but we have been unable to get any history which would indicate that the patient had had any contact with any suspicious case.

Up to the present, there is no clue as to how the infection may have been acquired. The woman not only had not been in the tropics, but had lived a relatively isolated life. Some years ago there was employed on the farm a man who as a sailor had been in the Philippines and other tropical ports, but who apparently was in good health. There is hardly the remotest possibility that he may have been the source of the infection.

Summary.—The disease designated by Darling, 1906, as histoplasmosis has been known only from the three cases reported by him, those of a Chinese and two Martiniquan negroes in the Ancon Hospital, Panama. A fourth case is here reported, that of a woman who had lived for forty-two years in Minnesota. This case was characterized by splenomegaly, moderate emaciation, anemia and a low fever. The lungs showed the characteristic granulomas described by Darling.

In sections of lungs, liver, lymph nodes, suprarenals and spleen, foci of chronic proliferative inflammation with areas of hyaline degeneration and giant

cells were frequently noted. There was a striking increase in large endothelial cells. These endothelial cells were in most instances filled with minute organisms corresponding to Darling's *Histoplasma capsulatum.*

Cultural studies were not possible since the organisms were not noted until some weeks later.

There is no indication of the source of the infection.

THE SOCIETY OF AMERICAN BACTERIOLOGISTS

Twenty-Seventh Annual Meeting, Madison, Wis., Dec. 29, 30, 31, 1925

Norman MacL. Harris, President; J. M. Sherman, Secretary, Cornell University, Ithaca, N. Y.

SECTION ON COMPARATIVE PATHOLOGY AND IMMUNOLOGY

F. M. HUNTOON, *Chairman*

STUDIES ON THE ETIOLOGY OF DISTEMPER IN FOXES. R. G. GREEN and H. O. HALVORSON, Medical School University of Minnesota.

Epidemics have occurred on silver fox ranches entailing a mortality as high as 70 per cent. The most common lesions have been pneumonia, intestinal lesions and an enlarged spleen, with a general toxic effect on all organs.

In some epidemics pneumonia occurred only occasionally, with the upper respiratory tract normal. The blood, abdominal organs and central nervous system were found to contain the virus. Filtration experiments showed the infective agent to be nonfiltrable. The most constant bacteriologic finding was the presence of members of the *Salmonella* group. They appeared in pure culture in most ranch foxes. They occurred in pure culture almost always when the disease was transmitted by injection of infective material.

Pure cultures of *Salmonella* obtained from foxes were pathogenic and would cause death in from twelve days to thirty days, producing the typical disease. After injection the organism can be recovered in pure culture at necropsy.

CHANGES IN INTESTINAL FLORA OF RATS ON A CALCIUM DEFICIENT DIET. RACHEL E. HOFFSTADT and SYLVIA J. JOHNSON, Department of Bacteriology, University of Washington.

Twenty-six hooded and white rats were fed on a diet deficient in calcium and ten on the same diet with calcium supplied. Fecal examinations were made at intervals of seven days for total bacterial count and types of aerobic and anaerobic organisms present. Necropsies at death were performed on all animals. It was found that the calcium deficient diet caused a definite constipation as shown by physical symptoms and a lowered bacterial count. This may or may not have coincided with the appearance of rickets, depending on the initial physical condition of the animals. The types of organisms present were not different in either group of rats. No gross pathologic changes were noted, except an apparent thinning of the wall of the small intestine.

L. Acidophilus in Epilepsy. N. Kopeloff, M. P. Lonergran and P. Beerman, Psychiatric Institute, Ward's Island, N. Y.

Owing to the importance of the gastro-intestinal tract in epilepsy, the investigation of *L. acidophilus* in this condition was undertaken. A series of fifteen epileptic patients were carefully observed for one month, following which twelve of these (the other three had only one convulsion per month or less) were given 1 liter of sterile milk for forty-two days. The methods employed here have been described in "Lactobacillus Acidophilus" (Williams & Wilkins Co., Baltimore, 1925).

Ingestion of sterile milk did not influence the number of convulsions. Neither did the ingestion of 60 Gm. of kaolin daily for one month. But when the same quantity of *L. acidophilus* milk, 1 liter reinforced with 300 Gm. of lactose, was administered for two months, there was a striking reduction in the number of convulsions in five patients. A slight reduction was also noted in four other patients. Three patients remained the same, and one showed a slight increase in the number of convulsions.

In the two-month period following the administration of *L. acidophilus* milk, all the patients (with one exception) had an increased number of convulsions. It appears, therefore, that the treatment was not sufficiently prolonged to confer permanent benefit. However, the results are encouraging enough to continue the treatment on a larger series of patients. This is now being done as well as the repetition of the foregoing experiments on the same patients.

The Influence of L. Acidophilus on the Colon-Aerogenes Group in the Intestine. Nicholas Kopeloff and Philip Beerman, Psychiatric Institute, Ward's Island, N. Y.

L. acidophilus has been shown to reduce the *relative* numbers of the colon-aerogenes group in the intestine, but the question of *actual* reduction is a perplexing one. The present study was carried out on a series of thirty-six epileptic patients under daily observation. Fecal examinations were made weekly for seven months, comprising the periods before treatment, administration of sterile milk or kaolin, *L. acidophilus* milk, and after treatment. Platings were made on whey agar and the Ayers and Rupp synthetic medium for the enumeration of the colon-aerogenes group. The fecal specimens were dried and proper calculation for moisture made.

The results proved to be extremely variable, since the patients were on the routine hospital diet. In fact, it was impossible to arrive at any clear-cut conclusions because of the large experimental error. In general, it may be said that in about one-half the instances an actual reduction in numbers of the colon-aerogenes group was obtained when averages were computed. The problem, therefore, cannot as yet be regarded as solved.

Experimental Bacillus Pyocaneus Keratitis. Edna Jackson and F. W. Hartman, Henry Ford Hospital, Detroit, Mich.

The virulent strain of *B. pyocaneus* used in this work was isolated from a group of industrial cases of keratitis.

The bacillus was isolated from only seven of eighteen cases all clinically similar. In some *B. pyocaneus* was isolated along with *Staphylococcus aureus*, and only the reproduction of the rapidly spreading digesting lesions in rabbits convinced us that the former was the etiologic factor. Injection of the culture between the layers of the cornea was the only method of infection which reproduced the disease.

Since the only effective treatment of the lesions was the destruction with the cautery, it seemed worth while to investigate the possibility of active and passive immunity in the rabbit. Results of the serum treatment of the disease in rabbits will be reported.

CLADOTHRIX ISOLATED FROM THE GENITO-URINARY TRACT. SARA A. SCUDDER and DAVID L. BELDING, Evans Memorial, Boston, Mass.

Three strains of *Cladothrix*, as yet unidentified, have been isolated from the genito-urinary tract. Strain A was obtained from the cervix of a child. Strains B and C were obtained in almost pure culture from the prostatic secretion of patients who had clinical signs of chronic urethritis with no clinical or laboratory evidence of gonorrhea. When first isolated, all three strains morphologically and culturally resembled long-chained streptococci, but under favorable conditions of growth, they showed a marked pleomorphism, varying in form from streptococcus-like chains to long wavy filaments with transverse constrictions and branching. The filaments, which varied from 0.6 to 1.7 microns in diameter and 2.2 to over 100 microns in length, showed definite protoplasmic differentiation when stained by an alkaline modification of Gram's method. Lancet-shaped diplobacilli were present in the young cultures and large globoid bodies were observed frequently in the old cultures. The strains grew well in broth which had a reaction from p_H 6.8 to p_H 8, the tangled threads forming fluffy masses which were either suspended in the fluid or adherent to the sides of the tube. In broth which had a reaction over p_H 7.6 the long strands interlaced in a weblike formation and if undisturbed, remained suspended from the meniscus. The three strains were similar in carbohydrate fermentation, but different in the quantity and rapidity of acid production. In contrast to the other two, strain C had shorter chains, produced greater cloudiness in broth, formed acid more rapidly, and presented minor serologic differences.

A SIMPLE MODIFICATION OF THE BRILLIANT GREEN METHOD OF ISOLATING BACTERIUM TYPHOSUM FROM FECES. MORRIS L. KAKIETEN and LEO F. RETTGER, Yale University.

The method is essentially that of Browning, Gilmour and Mackie, and used by Robinson and Rettger in their earlier work. The only real departure is the use of a buffer in the brilliant green peptone solution which constitutes the preliminary enrichment medium. The stock buffer employed was a mixture of 7.5 Gm. each of KH_2PO_4 and K_2HPO_4 in 155 cc. of distilled water. Of this solution 0.4 cc. was added to 5 cc. peptone solution, or 1 per cent. The buffered brilliant green peptone tubes had a hydrogen ion concentration of p_H 6.5. The amount of buffer used was sufficient to keep the p_H below 7 and thus prevent the removal of the brilliant green from solution during the incubation period. Platings were made from the enrichment tubes after from eighteen to twenty-four hours' incubation at 37 C. on the modified Endo medium of Robinson and Rettger.

This method was employed on more than 200 samples of feces which were artificially infected with *Bacterium typhosum* with consistent results. In addition, it was used by the authors in the isolation of *Bacterium typhosum* at the Lenox Hill Hospital, New York, during the typhoid epidemic in the fall of 1924. In the bacteriologic examination of the stools of fourteen clinical cases isolations were obtained in 70 per cent of the cases. Seven different brands of brilliant green were employed. Grübler's and one of the American brands were the most satisfactory.

THE USE OF GLYCEROL IN BRILLIANT GREEN BILE FOR THE ISOLATION OF B. TYPHOSUS FROM FECES. SOPHIE A. DEHLER and LEON C. HAVENS, State Board of Health, Montgomery, Alabama.

Brilliant green bile does not inhibit bacterial growth in some specimens of feces, thus making difficult the isolation of *B. typhosus,* if present, in such specimens. It was found that the addition of glycerol prevents, to a greater extent, the growth of all fecal bacteria. Various percentages (10 to 30) of glycerol in bile were tried. Difco bile dissolved in 10 per cent and 15 per cent glycerol in distilled water, with various concentrations of brilliant green, did not cause appreciably greater inhibition than the brilliant green bile without glycerol. Twenty per cent and 30 per cent glycerol caused marked inhibition of the fecal flora. Further experiments showed that 20 per cent glycerol bile containing brilliant green in the concentration of 1:10,000 did not inhibit *B. typhosus,* but prevented over-growth of fecal organisms. Plates streaked with a loopful of this medium containing feces artificially inoculated with small numbers of typhoid bacilli were rarely overcrowded, and frequently typhoid colonies predominated.

The advantage of this medium is the increased ease and accuracy in examining the plates, due to the marked inhibition of the fecal bacteria and the increase in the numbers of typhoid bacilli.

IMMUNOLOGIC STUDIES IN TUBERCULOSIS. IV. CONCERNING THE RESISTANCE TO INFECTION OF ANIMALS SENSITIZED WITH KILLED TUBERCLE BACILLI. S. A. PETROFF and F. W. STEWART, Research and Clinical Laboratory, Trudeau Sanitarium.

Guinea-pigs sensitized with dead tubercle bacilli were rendered skinsensitive to tuberculin. At the height of the tuberculin reaction they were inoculated with living tubercle bacilli. Such animals showed an increased resistance over normal controls inoculated at the same time and kept under the same conditions.

A NEW METHOD FOR SUSPENDING AND COUNTING LIVING TUBERCLE BACILLI. FREDERIC B. JENNINGS, JR., Research and Clinical Laboratory, Trudeau Sanitarium.

Living organisms are suspended in buffer solution, filtered through paper, and counted in a bacterial counting chamber. Such suspensions are free from clumps, do not agglutinate spontaneously, and the counting is simple and accurate.

A STUDY OF THE BLOOD GROUPS AMONG THE AMERICAN INDIANS. CLARA NIGG, Department of Bacteriology, University of Kansas.

A study of 800 American Indians shows an incidence of group 1 blood grouping of from 70 to 72 per cent.

DATA BEARING ON THE QUESTION OF THE SIZE OF THE ANTIBODY MOLECULE AND THE AMOUNT OF ANTIBODY SUBSTANCE PRESENT IN AN IMMUNE SERUM. F. M. HUNTOON, Research Laboratory, H. K. Mulford Co., Glenolden, Pa.

Calculations based on the total solids and nitrogen content of antibody solutions not only enable the placing of a limit to the amount of antibody substance present but in the case of agglutinins establishes an outside limit of the size of the molecule of 31 millimicrons.

PRECIPITATION WITH FRACTIONS OF SYPHILITIC SERUM. PEARL L. KENDRICK and R. L. KAHN, Department of Health, Lansing, Michigan.

An attempt was made to determine what fraction of syphilitic serum contained the reacting substances responsible for precipitation. The serum fractions were obtained by various degrees of saturation with ammonium sulphate. The precipitin reacting substances were determined quantitatively by means of the Kahn test.

Preliminary experiments indicated that the globulin fraction of syphilitic serum obtained after 33.3 per cent saturation with ammonium sulphate contained less of the precipitin substances than the original serum; the fraction obtained after 40 per cent saturation contained almost the same amount and the 50 per cent fraction, the same amount as the serum.

Comparative determinations of the precipitin substances were then made with the fractions obtained after 50, 75 and 100 per cent ammonium sulphate saturation and the original serum. It was observed that all these fractions as well as the original serum were of approximately the same potency, indicating that the albumin fraction was free from precipitin substances. This observation was corroborated by negative findings given by the albumin fraction obtained after completely saturating the supernatant fluid of the 50 per cent globulin fraction.

These findings indicate that the globulin fraction of syphilitic serum obtained after 50 per cent saturation with ammonium sulphate contains all the reacting substances responsible for positive precipitations as determined by the Kahn test.

THE EFFECT OF CERTAIN SUBSTANCES ON THE PRECIPITIN REACTION. CORNELIA M. DOWNS and KENNETH GOODNER, Department of Bacteriology and Immunology, University of Kansas, Lawrence, Kan.

In the precipitin-preciptinogen reaction the presence of foreign protein does not increase the prozone nor inhibit the reaction.

The precipitate dissolves in weak carbonate solutions. Preciptinogen is present in the fluid but no precipitin is detectable until the solution is neutralized. The precipitate is completely dissolved in 40 per cent dextrose with the appearance of both precipitin and precipitate in the solution.

A RAPID METHOD FOR THE MACROSCOPIC AGGLUTINATION TEST. ARLYLE NOBLE, Medical Research Department, Parke, Davis and Company, Detroit, Mich.

Using concentrated antigen, with small quantities of serum and antigen, shaking is substituted for incubation. Readings are made in from twelve to twenty minutes.

PLACENTAL TRANSMISSION OF FOREIGN PROTEIN. FRANCES E. HOLFORD, University of Wisconsin.

The placental transmission of foreign protein is under investigation. By precipitin tests on the serum of the new-born, transmission of crystalline egg albumin injected subcutaneously near term has been demonstrated both in normal and in highly immunized rabbits.

EXPERIMENTS ON THE SOLUBILITY OF PNEUMOCOCCI IN BILE AND IN SODIUM OLEATE SOLUTIONS. I. S. FALK and S. Y. YANG, University of Chicago.

We have found that washed suspensions of pneumococci in distilled water are usually bile soluble. An occasional preparation is refractory to the solvent action of the bile. The chlorides with monovalent cations (Na, K, NH_4, Li)

in relatively low concentrations inhibit the dissolution of washed pneumococci by bile; in higher concentrations these chlorides do not inhibit, indeed, may accelerate the dissolution of the bacteria. Chlorides with divalent cations (Ca, Ba) behave quite differently. They are found to inhibit bile solution of pneumococci more effectively in high than in low concentrations. Of the anion series tested, NaOH and Na_3PO_4 are cytolytic to pneumococci; Na_2HPO_4, NaH_2PO_4, Na_2SO_4 and $NaNO_3$ are not cytolytic. Cytolysis by NaOH and by Na_3PO_4 appears to be a function of the hydroxyl ion concentration. Peptone, gelatin and ovalbumin appear to inhibit cytolysis by bile in the same manner as $CaCl_2$ and $BaCl_2$. The inhibitory action increases with concentration. The differences in the behavior of chlorides of monovalent and divalent cations recorded here appear to be in harmony with the usual findings in general physiology, whether effects upon animals and animal tissues, upon chlorophyll-bearing plants, bacteria or on nonliving substances are studied.

In the concentrations in which it is active (1.25 per cent and higher) sodium oleate dissolves only pneumococci of those strains which are also dissolved by bile. In effective concentrations, sodium oleate, in aqueous solutions, dissolves washed pneumococci resuspended in distilled water; it does not dissolve pneumococci which have been resuspended in 0.85 per cent NaCl solution or in the supernatant of the culture fluid from which they had been separated by centrifugalization. The bacteriolysis of washed pneumococci by sodium oleate, sodium hydroxide or by sodium phosphate (tribasic) is as specific as lysis by bile. Suspensions of bile insoluble strains of pneumococci, of strains of *Streptococcus hemolyticus, Str. viridans, Str. lacticus, M. catarrhalis, Sarc. lutea, Staph. albus* and of *Staph. aureus* are not dissolved by these reagents.

ACTION OF ULTRAVIOLET LIGHT ON THE ANTIGENIC PROPERTY OF P. AVICIDA. L. D. BUSHNELL.

Ultraviolet light has a deleterious effect on the antigenic properties of *P. avicida* as compared to the effect of heat killed cultures.

THE FATE OF BACT. TYPHOSUM AND OTHER ORGANISMS IN A SEGREGATED VEIN AND IN THE GENERAL CIRCULATION OF THE NORMAL AND IMMUNIZED RABBIT. RALPH G. MILLS and GAIL M. DACK.

A marked reduction of the bacterial count followed the introduction of organisms both in the segregated vein and in the general circulation. The rate of reduction differed, however. It is suggested that an additional factor is involved in the destruction in the general circulation, possibly the phagocytic power of fixed tissue cells.

NOTES ON THE BACTERIOLOGY OF TWO CASES OF UNDULANT FEVER IN MAN. CHARLES M. CARPENTER, Department of Pathology and Bacteriology, Cornell University, N. Y. State Veterinary College.

This is a discussion of the occurrence of *Brucella abortus* in man, with a bacteriologic report of two cases of undulant fever.

IS BACT. ABORTUS (BANG) PATHOGENIC FOR MAN? I. FORREST HUDDLESON, Michigan Agricultural Experiment Station, Michigan State College.

The writer reports three cases of recurrent fever in young men during the past year and evidence which incriminates *Bact. abortus* as being the causative agent.

In the first case, no hemo or urine culture was made, but the agglutinin titer of the blood serum was found to be 1:400 one year after the appearance of clinical symptoms. This case resembled the ambulatory type of recurrent fever.

The second case clinically resembled the typical type of recurrent fever. The blood serum, one week after the appearance of clinical symptoms, showed an agglutinin titer of 1:1000 for both *Bact. abortus* and *melitensis*. An organism was cultivated from the blood in atmosphere containing 10 per cent carbon dioxide which resembled *Bact. abortus* culturally and serologically.

The third case resembled the ambulatory type of the disease. The blood serum shows an agglutinin titer of 1:200 and positive culture. All three of the young men have worked with *Bact. abortus* in the laboratory. The patient in case 3 has also worked with *Bact. melitensis*.

The second and third patients had been drinking raw milk for some time from the same source. The raw milk contained *Bact. abortus* in large numbers.

A Method of Increasing the Virulence of Cultures of Clostridium chauvoei by the Use of Ferric Salts. Joseph P. Scott, Kansas Agricultural Experiment Station, Manhattan, Kansas (read by Dr. L. D. Bushnell).

The addition of ferric sulphate or ferric chloride to Hall's medium caused a marked increase in the virulence of strains of *Clostridium chauvoei* inoculated on such mediums.

Generalized Torula Infection in Man. B. Z. Rappaport and Bertha Kaplan, University of Illinois, College of Medicine.

A study of the thirteenth case of torula infection in man reported in the literature. Clinically a chronic meningitis, diagnosed antemortem by positive blood and spinal fluid cultures. Report of the pathologic findings. (Will be published in full in Arch. Path.)

Influence of B. Welchii Toxin on Erythrocytes in Vivo and in Vitro. Guilford B. Reed and J. H. Orr, Queen's University, Kingston, Canada.

B. welchii toxin injected intravenously into rabbits produces rapid destruction of red blood cells. If the dose of toxin is large the destruction is rapid and may be followed by the death of the animal. If the dose is smaller the destruction is less rapid and the anemia may be transient. In either case, however, the red cell destruction is accompanied by a profound alteration in the structure of the cells characterized in the first stages of the toxemia by an increase in microcytes followed later by an increase in macrocytes, poikilocytes, polychromatophilia and budding cells.

Similar changes are observed when *B. welchii* toxin is mixed with defibrinated blood or with washed erythrocytes suspended in physiologic sodium chloride.

Pernicious Anemia-Like Blood Changes Accompanying B. welchii Infections in Rabbits. Guilford B. Reed and J. H. Orr, Queen's University Kingston, Canada.

A virulent *B. welchii* culture kept for several days in the icebox and injected in suitable numbers into rabbits subcutaneously, intramuscularly or intravenously produces an infection which may terminate fatally in from twelve hours to three weeks or may persist for from two to five weeks and may be followed

by apparently complete recovery of the animal. Such infections in rabbits are always followed by an anemia the extent of which is roughly proportional to the activity of the infection.

When the *B. welchii* infection is very active there is a marked decrease in the number of circulating erythrocytes, an increase in the color index and a profound alteration in the structure of the red cells characterized by anisocytosis, poikilocytosis, polychromatophilia and nucleated red cells. Where the infection is less active there may be no decrease in red cell count but at the same time a measurable anisocytosis and poikilocytosis.

HEMOLYTIC STREPTOCOCCI OF THE BETA TYPE IN CERTIFIED MILK. J. HOWARD BROWN, W. D. FROST and MYRTLE SHAW, University of Wisconsin.

Over 90 strains of beta hemolytic streptococci were isolated from the cows and mixed milk of a number of certified milk herds including about 900 cows. There was nothing abnormal about the condition of these dairies and the milk is not known to have caused any infection in the consumers. The streptococci were carefully studied in comparison with strains of *Streptococcus epidemicus* from most of the well studied milk-borne epidemics of septic sore throat which have occurred in the United States since 1911. All the strains of *S. epidemicus* were found to be alike in being encapsulated, in producing rapid hemolysis of red blood cells in fluid mediums, in being pathogenic for mice, in producing a final hydrogen ion concentration not higher than p_H 4.8 in glucose broth, in fermenting salicin but not mannite, and in failing to hydrolyze sodium hippurate. All of the bovine strains differed from *S. epidemicus* in one or more of the foregoing characters. There is no evidence that any of them are pathogenic for man. No known single test is sufficient to differentiate the bovine strains from those which may be pathogenic for man.

Hemolytic streptococci, nonpathogenic for man, are to be found in the milk of many clinically normal cows and probably in the mixed milk of all herds of more than a few cows.

The streptococcus of milk-borne septic sore throat is a well defined species or variety which may be distinguished from other hemolytic streptococci found in milk by the tests described. It retains its characters unchanged during years of cultivation in the laboratory.

STUDIES ON THE STREPTOCOCCUS OF EPIDEMIC ENCEPHALITIS. ALICE C. EVANS and WALTER FREEMAN, Hygienic Laboratory, Washington, D. C.

A streptococcus was obtained from the nasal washings during life and from the midbrain and heart blood taken at necropsy from a human case of epidemic encephalitis. This streptococcus is highly virulent for rabbits when inoculated into the brain, causing death in from five and three-quarters to eighteen hours when the inoculating dose is 0.25 cc. of undiluted broth culture. When inoculations were intracerebral the minimal lethal dose was found to be 0.25 cc. of culture diluted 1:10,000. Occasionally infection followed heavy intravenous inoculations. In that case the brain was always found to be heavily seeded with the streptococcus.

Filtrates of an emulsion of the human brain, of the emulsions of rabbits' brains and filtrates of cultures have given uniformly negative results when inoculated directly into the brains of rabbits. By planting the filtrates in meat medium, however, virulent cultures have been obtained repeatedly, and they have shown that the organism is in a filtrable form in the human brain, in the rabbit brain, and in cultures.

The experimental disease produced in rabbits and monkeys closely resembled epidemic encephalitis of man. The symptoms and histologic lesions are discussed.

The same streptococcus was also obtained from the nasal washings, or saliva, or both, from all of the three other patients examined, who were suffering with the chronic form of the disease and from the throats of normal persons.

Serologic tests have not yet been made.

The streptococcus here described was identified with the organism obtained from a human case and described by von Wiesner as the cause of epidemic encephalitis. It agrees also with the streptococcus which Rosenow has obtained repeatedly from human cases. Culturally there is no characteristic which would distinguish it from an ordinary *Streptococcus viridans,* but morphologically it exhibits a variety of characteristic pleomorphic forms.

FURTHER STUDIES ON THE POLIOMYELITIS PRECIPITIN REACTION. E. C. ROSENOW, Department of Experimental Bacteriology, Mayo Foundation, Rochester, Minnesota.

In this study previous findings are corroborated.

The incidence of a positive precipitin reaction at the time of attack of poliomyelitis was almost 100 per cent whereas the reaction almost always became negative within three weeks after onset of attack. The results in persons having abortive attacks were similar. The incidence of positive reactions in normal contacts was 77 per cent; in normal controls within the epidemic zone, 72 per cent; outside of the epidemic zone, 18 per cent; and in isolated family groups at the time of epidemics, on the average about ten times as high as after the epidemic had disappeared. A positive precipitin test with swabbings from the throat indicates the presence of the characteristic streptococcus as determined by agglutination reactions and the production of flaccid paralysis in animals.

THE PRECIPITIN REACTION IN THE DIAGNOSIS OF SCARLET FEVER AND ALLIED HEMOLYTIC STREPTOCOCCUS INFECTIONS. E. C. ROSENOW, Department of Experimental Bacteriology, Mayo Foundation, Rochester, Minnesota.

The precipitin reaction with an immune serum, prepared by the intravenous injection of first the dead bacteria and then living cultures of the hemolytic streptococcus from scarlet fever, has been found valuable in differentiating ordinary hemolytic streptococcus infection of the throat and infections due to scarlatinal hemolytic streptococci. A close agreement was found between the results of the precipitin reaction and the production of toxin neutralizable by scarlatinal immune serums. Infection of the throat due to scarlatinal hemolytic streptococci was found common at the time of an epidemic in persons who had had attacks of scarlet fever and others in whom the Dick skin test was negative. A close relationship has also been found between virulence and toxin producing power, and scarlatinal and other hemolytic streptococci. Some of the former lost toxin producing power and some of the latter acquired the power to produce toxin neutralizable by scarlatinal antistreptococcus serum.

TOXIN PRODUCTION OF STREPTOCOCCUS ERYSIPELATIS. KONRAD E. BIRKHAUG, Department of Bacteriology, School of Medicine and Dentistry, University of Rochester, Rochester, N. Y.

The toxins employed in these studies were prepared in Douglas' tryptic medium inoculated with cultures of *Streptococcus erysipelatis,* which were

isolated from the erysipelatous lesions of patients ill with erysipelas. Among thirty-four strains grown at 37 C. for periods varying from six to ninety-six hours, the maximum toxin production was obtained in lots incubated for about forty-eight hours. Each of the thirty-four strains studied were found to yield uniformly toxic filtrates. A skin test dose of 0.1 cc. of a 1:1000 dilution of erysipelas toxic filtrate produced in the skin of susceptible persons a lesion, similar in nature to that obtained in the Schick and Dick tests, which measured more than 1.5 cm. in diameter. Complete neutralization of one skin test dose of the erysilepas toxin was obtained by mixing it with an equal amount of convalescent erysipelas serum, or with 0.001 cc. of erysipelas antistreptococcic rabbit or donkey serums. Neutralization of the erysipelas streptococcic toxin was not accomplished by Dochez' scarlatinal antistreptococcic serum, nor by normal rabbit or donkey serums. During the acute stages of erysipelas the patient's blood serum and urine contained a toxic substance which was completely neutralized by convalescent erysipelas serum and which disappeared from the patient's blood serum and urine as soon as twelve hours after the administration intramuscularly of 25 to 100 cc. of erysipelas antistreptococcic rabbit or donkey serums. If the disease persisted unchecked by the serum therapy, the skin reaction remained positive until defervescence and definite regression of the erysipelatous lesion occurred.

Positive skin reactions were obtained by one skin test dose of erysipelas streptococcic toxin in 27 per cent of apparently normal adults and in 21 per cent of normal school children. Among nineteen persons with definite histories of single and recurrent attacks of erysipelas, four persons gave positive reactions with one skin test dose of the erysipelas streptococcic toxin. These findings add further evidence to our previous reports that a specific relationship exists between *Streptococcus erysipelatis* and erysipelas.

STUDIES ON SCARLET FEVER TOXIN. PAUL F. ORR and M. S. MARSHALL, State Department of Health, Lansing, Mich.

Scarlet fever toxin was produced in accordance with the procedures of the Drs. Dick from a selected group of strains of hemolytic streptococci isolated either from the throats of scarlet fever patients, or from postscarlatinal discharging ears.

Twenty or thirty minutes' exposure of the toxin at 100 C. usually rendered it atoxic; however, at least forty-five minutes is necessary to insure 100 per cent negative controls in the skin test. Culture medium, treated as in the preparation of toxin, except for the inoculum, gave no reaction in any skin tests in which it was used as a control. It is not considered as good a control as heated toxin.

The age grouping of individuals susceptible to scarlet fever as evidenced by a positive Dick test showed a maximum susceptibility at from 2 to 4 years of age. However, the number of tests on children under 3 years was relatively small, and it is possible that the maximum susceptibility may occur in a younger age group. An average of 34 per cent of positive Dick reactions was obtained in individuals of all age groups in state institutions.

Little difficulty was experienced in reading skin tests on colored children.

Some work has been done by the state health department of Michigan on the dosage of toxin necessary for immunization, demonstrating the necessity for a large number of skin test doses for injection subsequent to the first.

IMMUNIZATION AGAINST DIPHTHERIA AND SCARLET FEVER WITH TOXINS DETOXIFIED WITH SODIUM RICINOLEATE. W. P. LARSON, Department of Bacteriology and Immunology, University of Minnesota.

This paper discusses mechanism of detoxification; quantitative relationship between toxin and soap; effect of concentration of both toxin and soap; the effect of dilution on a neutral soap toxin mixture; results of animal experimentation; results of active immunization against diphtheria and scarlet fever; the possibility of suppressing epidemics of scarlet fever by active immunization.

THE BACTERIOLOGY OF CHRONIC PROSTATITIS AND THE LOCALIZATION IN ANIMALS OF ORGANISMS ISOLATED. A. C. NICKEL, Department of Experimental Bacteriology, Mayo Foundation, Rochester, Minnesota.

This paper takes up, first, the bacteriology of chronic prostatitis as reported by various investigators, and then compares those bacteriologic findings with the results obtained by the author. A further study is made of the relation of chronic prostatitis to systemic conditions and to other foci of infection, and the causal relation of the bacteria to these conditions as found by experimentation is based on the elective localizing power of the microbe in inoculated animals.

THE DISTRIBUTION OF FUSIFORM BACILLI AND SPIROCHETES IN TISSUE. I. PILOT, University of Illinois, College of Medicine.

In pathologic lesions the fusiform bacilli and spirochetes have often a characteristic distribution. The bacilli lie in the necrotic portion while the spirochetes are seen advancing from the margins into the surrounding tissues.

Book Reviews

ALLERGY, ASTHMA, HAY FEVER, URTICARIA AND ALLIED MANIFESTATIONS OF REACTION. By WILLIAM W. DUKE, PH.B., M.D. Cloth. Pp. 339, with 75 illustrations. St. Louis: C. V. Mosby Company, 1925.

The subject matter is divided into two sections. In the first and larger part there is a discussion of experimental anaphylaxis, serum sickness, bacterial allergy, followed by natural hypersensitiveness in man, pollen abundance, the agents which sensitize man, contributory causes, general characters and symptoms of the reaction, its diagnosis and treatment. The second part, comprising fifty-five pages, deals with what is referred to as physical allergy, including contact reactions caused by light, heat, cold and mechanical irritants, and reflex-like reactions caused by heat, cold and light.

The principal feature of advantage in this book is the discussion of the clinical features of allergic manifestations. The methods of examination and diagnosis are admirable and thorough. The methods of treatment are excellent and well described. The pathologic and experimental basis of the studies is largely in the form of quotations from Zinsser and Coca. This feature of the work, excellent so far as it goes, is, in this form, necessarily incomplete. The omission of a discussion of anaphylactoid phenomena is to be regretted, since a book for clinicians should cover this field in order to give a clear picture of allergy and similar but not identical processes. The inference that the physical agents, discussed in the second part, produce reactions of the same order as those ordinarily included in the term allergy, is premature and as yet without adequate foundation. Many of the other clinical syndromes are included as if they were of established allergic nature, and this assumption may lead to confusion on the part of the reader. Clinical investigations, such as those reported, should be subjected to the same critical analysis as are experimental data. If such criteria be applied, certain of the conclusions seem to rest on an unsatisfactory basis.

Errors that have escaped the proof reader, such as positive congestion for passive congestion, hormonize for harmonize, foul for fowl, antiseptics for anesthetics, disturb the reader and may be confusing. The section on plants and pollens is well illustrated, but many of the other illustrations give no information of real value. The bibliography is excellent.

HANDBOOK OF PATHOLOGY. By C. Y. WANG, M.D., Edinburgh, B.Sc.Vict., F.R.C.P. Edinburgh, Professor of Pathology in the University of Hongkong. New York: William Wood & Company, 1925.

This book of five hundred pages is an excellent compendium and probably a successful achievement of the author's "object of presenting in a short, concise form the more salient points in pathology, such as appear to the author to meet the main requirements of the students of medicine for whom it is primarily intended."

Professor Wang is a Chinese, and the students for whom the book is intended are presumably students of his own nationality in the University of Hongkong; therefore perhaps it is unfair to judge of the book with a viewpoint of a teacher in an American medical school. However, the reviewer sees no alternative.

Textbooks at their best are poor accessories to the teaching of pathology, and this instance is an example of a poor type, because, as stated in the preface, "except in a few instances theoretical discussions have been omitted, as have the subjects of congenital malformities, biology of bacteria and parasitology."

The work is crowded with statements of facts and definitions, and many pages are mere catalogs of conditions. There are 274 illustrations reproduced from photographs and photomicrographs; the majority of the latter are not good. The four colored plates, one of them on the blood, are decorative but not valuable.

Occasional statements, perhaps because of unfortunate wording, must be challenged. On page 12, in speaking of fatty degeneration we read "The change greatly impairs the function of the cell, tending to lead to its death." It hardly seems possible that the author confuses effect with cause! On page 53, hydrocephalus is referred to as edema in the ventricles of the brain without mention of the source, the cerebrospinal fluid. Under aneurysm, local weakening of the wall, we find that arteriosclerosis is given first place in etiology and that syphilis is mentioned together with alcoholism, gout, lead poisoning and other known or unknown toxins or poisons of a chronic nature, "among the causes the most common." Increase of blood pressure "is another important causal factor accompanying almost invariably arteriosclerosis or resulting from severe muscular strain." Under syphilis we find an incorrect account of the histologic sequences of syphilis of the aorta and a statement that the involved area "may afterwards yield to pressure and become stretched forming an aneurysm." Chapter X is entitled "Metaplasia." It consists of eight lines, practically a definition of metaplasia. The remainder of the page is blank.

The treatment of tumors is poor. Many statements can have no significance for the student; for example, on page 430 "Alveolar sarcoma is common in the skin, the lymph nodes, the bone, the muscles and the serous membranes. It is usually fairly malignant."

The reviewer has made no exhaustive search for inaccuracies. A few only are mentioned of those apparent in a hasty reading. On the whole the author has done well what he intended to do. As an aid in cramming for examinations the book should prove useful to students with good memories in tests in which thinking and correlation of facts are not required.

THE MELANOMATA, THEIR MORPHOLOGY AND HISTOGENESIS. JAMES W. DAWSON, Edinburgh and London, 1925.

This monograph largely from routine work at the Royal College in Edinburgh reprinted from the *Edinburgh Medical Review* for October, 1925, is as comprehensive a study of this class of tumors as has appeared in English. It is based on careful examination of 102 melanomas, 18 of them ocular; 38 acanthotic (prickle cell), pigmented nevi, all but one quiescent; other quiescent moles obtained postmortem and pigmented skin from various places, human as well as from lower animals.

The arrangement of the subjects dealt with; painstaking descriptions of microscopic structure; profusion of illustrations, some in colors, and bibliography are all in excellent balance and mark the work as masterly and authoritative.

It is not of paramount importance, but nevertheless a matter of regret, that melanomas primary in organs of the trunk and in the central nervous system were not available for inclusion in this study and for comparison with the more ordinary growths.

Two features of Dawson's work are of especial value. One is found in the accounts and illustrations of the early stages of active growth in pigmented moles, a multiplication of pigmented epithelial cells in the interpapillary epithelial processes which Dawson calls "rete epithelial processes." The other is the definiteness and air of finality in his advocacy of the epithelial and epiblastic origin of chromatophores. Although he uses such terms as melano-endothelioma, melanoperithelioma, melanosarcoma and melanofibrosarcoma, they are set off by quotation marks.

And because the origin of melanomas about which there has been so much controversy is taxonomically and for other reasons so important, one of the many statements illustrating the author's conviction may be quoted. Referring to the invasion of the corium by cells the product of proliferation in intra-epithelial nests, and to the absence of other changes in the corium preceding this invasion, he states that there can be "no other interpretation of the histogenesis of these tumour cells than a unity of conception which traces them, pigmented and non-pigmented, to an epidermal origin."

Some of the evidence for the genesis of chromatophores in epithelial cells in zoological literature, for example studies of the pigmentation of feathers, might also be included with advantage with that which Dawson has assembled.

Regarding the pigment, the author offers nothing new. Prominent mention is given to the views of Bloch regarding a colorless chromogen found only in epithelial cells and capable of being oxidized into melanin.

This work should meet a most cordial reception, for, as is well known, the relations of pigmented moles and melanomas generally are widespread at times commanding the utmost attention of practically all specialists in medicine and surgery. It should also find an important place of usefulness as a work of reference for students and teachers.

ESSENTIALS OF IMMUNOLOGY FOR MEDICAL STUDENTS. By ARTHUR F. COCA, M.D., Professor of Immunology in Cornell University Medical College. Cloth. Price, $3. Pp. 194, with 15 illustrations, 3 tables and 1 chart. Baltimore: Williams & Wilkins Company, 1925.

The subject of immunology is presented in a compass of 75 small pages, and the practical experiments are detailed in about 104 pages. The latter part of the book is its most valuable feature. The experiments are, in most instances, completely outlined, and with little supervision can be carried out well by the average medical student. The order of experiments is good and might readily be readjusted to meet the ideas of individual instructors. The subject matter of immunology is exceedingly brief and not so extensive as the chapters on this subject in several textbooks of bacteriology, pathology and hygiene. In fact, the brevity of discussions is in places so great as to sacrifice clarity. In the small compass of this book many statements necessarily savor of dogmatism. This may be justified when the authority of the writer is taken into consideration. Nevertheless, a book for general circulation should present controversial matters with less finality than is shown, as, for example, the basing of the anaphylactic reaction on the phenomenon of precipitation and the sharp separation of what the author calls atopy. The book is well printed, and the illustrations are excellent.

The reviewer cannot refrain from ardently supporting Coca's attitude toward the importance of immunology in the science and art of medicine, and agrees that this subject should be made an obligatory part of the medical curriculum.